

NorPEN

The Nordic Pharmacoepidemiological Network for
knowledge exchange, research and research training



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Nordic countries and pharmacoepidemiological studies

- Population of 24 million people
- Homogeneous
 - Genetically
 - Socioeconomically
- National health registries
- Public health care system (almost free of charge)
- Reimbursement of medicines for the whole population
- Personal Identification Numbers (PINs)

“The Nordic countries as a cohort” ICPE August 19, 2008 in Copenhagen

Pub Med

- Search terms
 - “Nordic countries epidemiology” 34 783
 - “Nordic countries pharmacoepidemiology” 110
 - 8 abstracts – comparisons of drug use

65 years



Nordic registers on dispensed medicines



2008

Nordic School of Public Health
Gothenburg, Sweden





Strong environment for
population based and
cross-country comparative research in
pharmacoepidemiology

Organisation

Steering group

Max Petzold, SE

Mette Nørgaard, DK

Morten Andersen, DK

Timo Klaukka, FI

Sirpa Hartikainen, FI

Magnús Jóhansson, IS

Kari Furu, NO

Gunilla Ringbäck Weitoft, SE

Helle Kieler, SE

Reference group

Prominent senior researchers
in epidemiology &
pharmacoepidemiology

Forum

Supervisors and PhD students

Collaborators

Database holders

Authorities

ENCePP

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- Document, facilitate and promote Nordic pharmacoepidemiological research initiatives
- Increase quality of research and methodological development
- Create an interactive forum for PhD-students and supervisors
- Assist researchers
 - Initiating and designing new studies
 - Improving quality
 - Avoiding common pitfalls and duplication of efforts

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- Research documentation
 - Annual reviews of published studies, research groups, centers working with the Nordic registers on dispensed medicines
- Voluntary pre-registration of register based studies within the Nordic countries
- Overview of organisation and content of the Nordic national registers
 - Process to obtain permission to access the register data
 - Identify obstacles to register based research
- Web-based system for publishing of basic information - www.nordically.org.

Prioritised research areas

- Rare exposures and rare events
- Prescribing quality indicators
- Reproductive health
- Medicine use in children
- Mental health

Meetings and workshops

1. March 2009, Gothenburg, Sweden

Kick-off meeting

Research with prescription medicine registers

Open invitation to Nordic researchers within the area

2. October 2009, Helsinki/Tampere, Finland

Reproductive health, medicine use in pregnancy

3. March 2010, Oslo, Norway

Prescribing quality indicators

Advanced methods for analysis of medicine use pattern in databases

4. October 2010, Reykjavík, Iceland

Medicine use in children

5. March 2011, Odense, Denmark

Rare exposures and rare events

6. October 2011, Gothenburg, Sweden

Mental health and psychotropic medicine use

Nordic study on SSRIs and risks of Congenital Malformations, Abortions, Perinatal Death and PPHN



Background

Congenital Malformations

Most studies found no statistically significant increased risks for congenital malformations in users of SSRIs

Major limitations in previous studies

- Low statistical power
- Uncertain information on exposure
- Exploratory analyses

Reported positive findings

Any SSRI

Malformations¹

Cystic kidneys²

Anencephaly³

Craniosynostosis³

Omphalocele³

ASD⁹

Sertraline

Omphalocele⁷

Septal defects⁷

Anal atresia⁷

Limb-reduction⁷

Fluoxetine

>2 minor anomalies⁴

Cardiovascular malformations⁸

Citalopram

>2 minor anomalies⁴

Cardiovascular malformations⁹

Paroxetine

Malformations^{5,6}

Cardiac malformations^{2,3,5,6,7}

Neural-tube defects⁷

Clubfoot⁷

¹Wogelius, 2006, ²Källén, 2007, ³Alwan, 2007, ⁴Chambers, 1996,

⁵GSK, 2005, ⁶Bérard, 2007, ⁷Louik, 2007, ⁸Diav-Citrin, 2008, ⁹Oberlander, 2008

Background

Persistent Pulmonary Hypertension of the Newborn

ICD -10
P29.3B

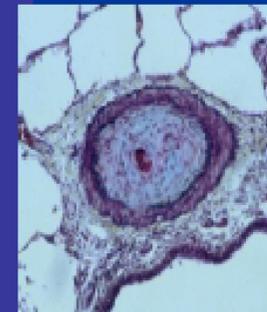
Term and
post-term infants

Incidence
1-2/1000

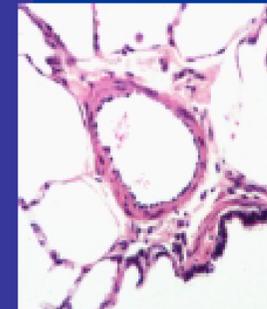
Mortality rate 15%



- Vasokonstriktion
- Mediaförtjockning hypertrofi, hyperplasi glatta muskelceller
- Proliferation av fibroblaster
- Deposition kollagen, elasatin
- Mikrotrombos, nekros, inflammation



PPH



normal

Reported findings

Persistent Pulmonary Hypertension of the Newborn

- 3 studies
 - Cohort study (Chambers, 1996)
 - 2.7% PPHN among Fluoxetine exposed compared with expected rate of 0.1%
 - Case control study (Chambers, 2006)
 - OR = 6.1 (95% CI 2.2 – 16.8)
 - Cohort study (Källen, 2008)
 - “RR” = 2.7 (95% CI 0.9 – 6.3)

Nordic study on SSRIs

- **Design**

Cohort study - 2 sub-studies

- **Data**

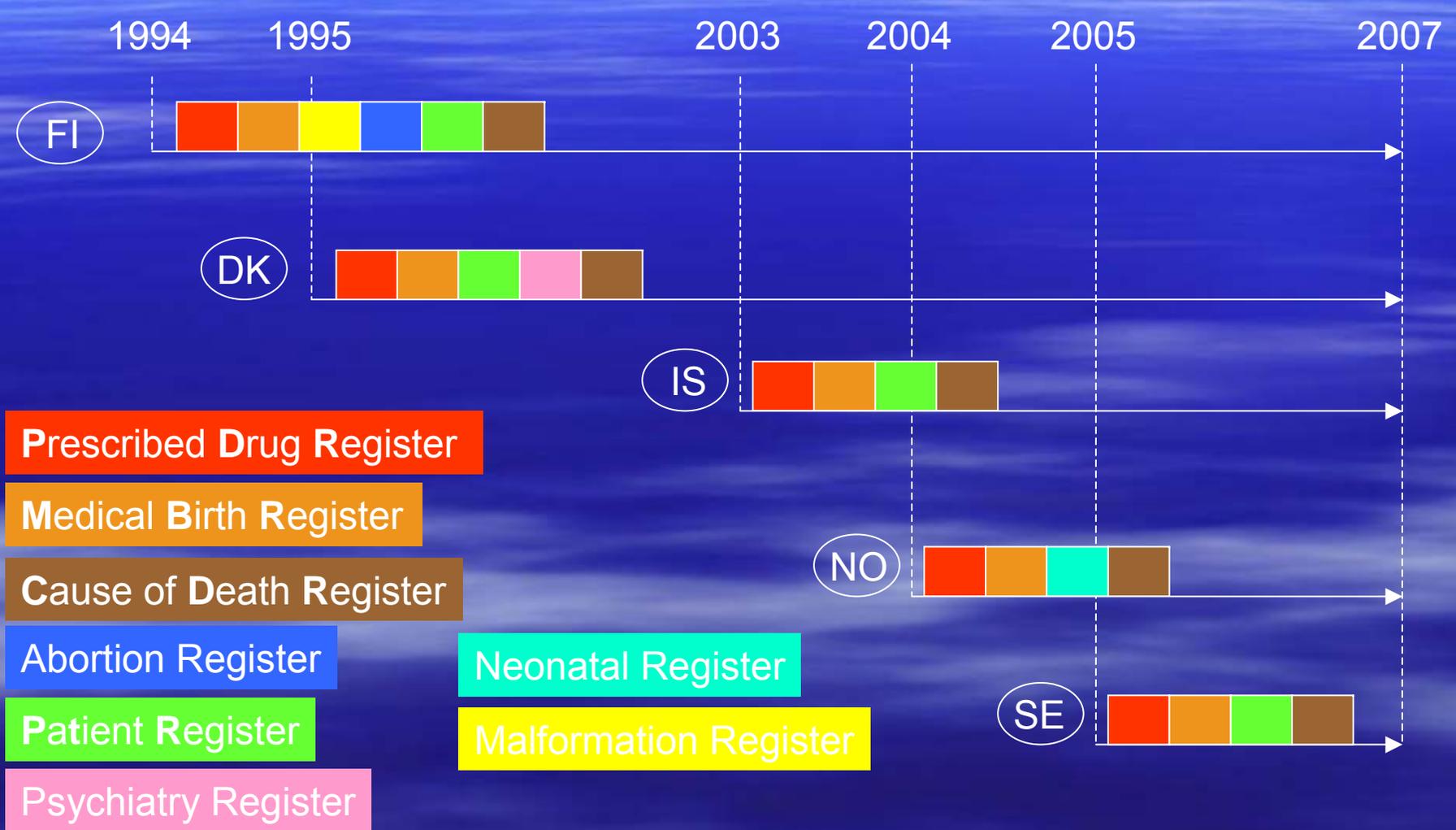
Nordic Health Registries

- Infants born in DK, FI, IS, NO or SE 1994-2007
- Abortions > Gestational week 13 (FI, NO, DK)

- **Outcomes**

1. Malformations, perinatal deaths, abortions
2. PPHN





FI - 1994

PDR (> 10 €)
MBR (†: gw 22, 500g+)
Malformation Register
Abortion Register (induced, + indication)
PtR
CDR

NO - 2004

PDR
MBR (†: gw 12, sp + induc abortions + indic,
“smoking”)
Neonatal Register
CDR

IS – 2003

PDR (÷ dosage)
MBR
PtR
CDR

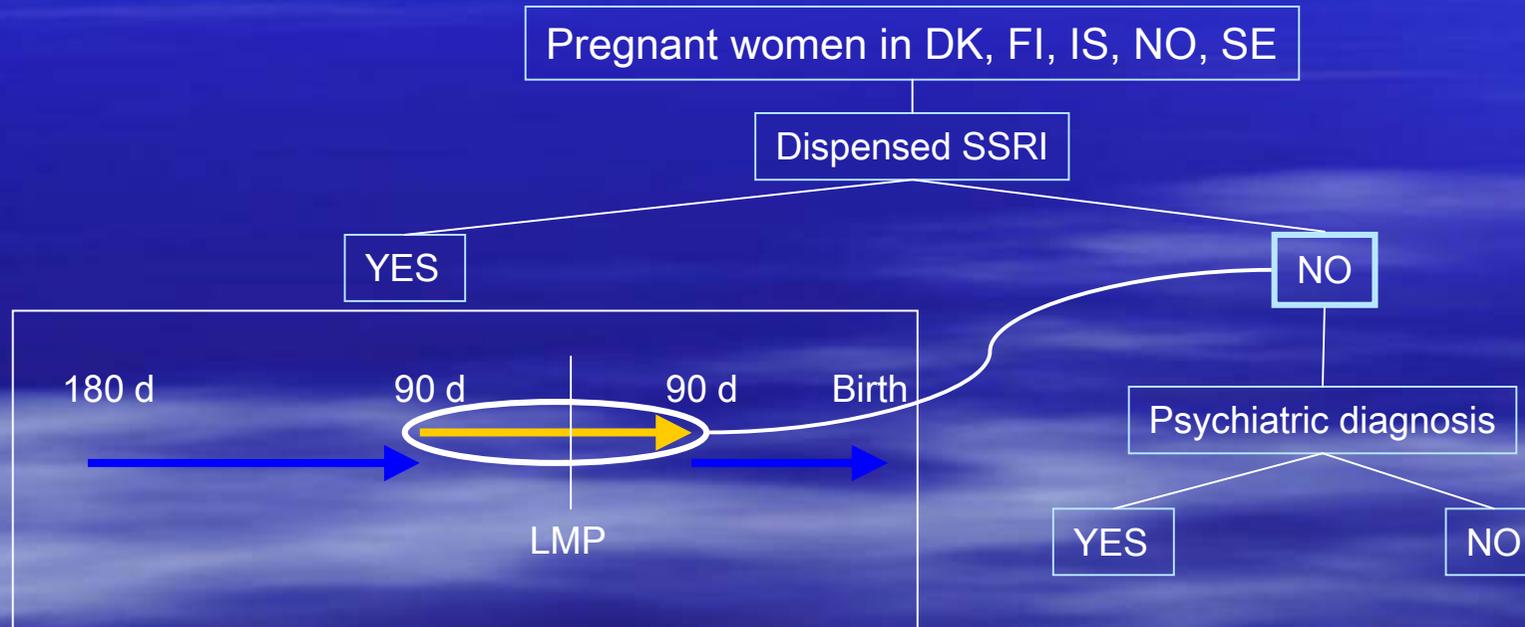
DK - 1995

PDR
MBR (†: gw 22, induced abortions, ÷ BMI)
PtR
Psychiatry Register
CDR

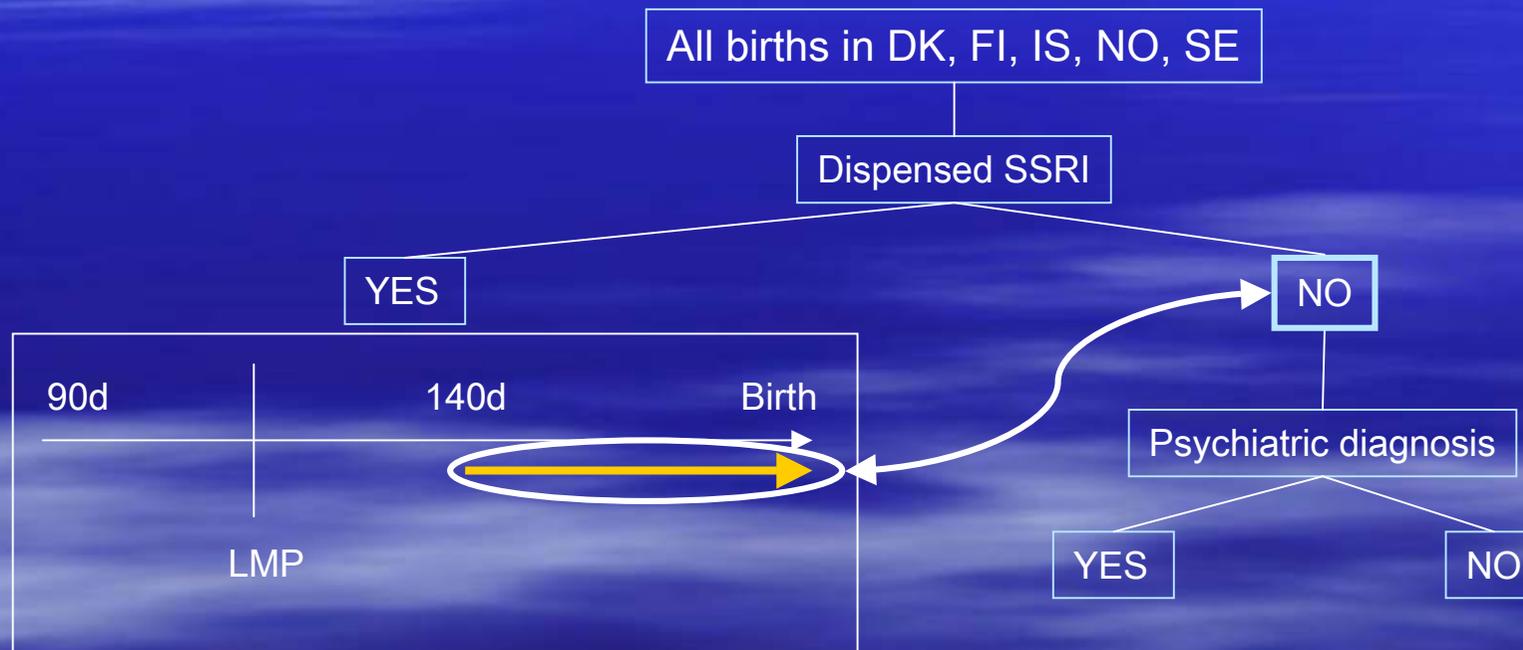
SE - 2005

PDR
MBR (†: gw 28, ÷ alcohol)
PtR (“psychiatric diagnoses”)
CDR

Congenital malformations, abortions



PPHN



3INF



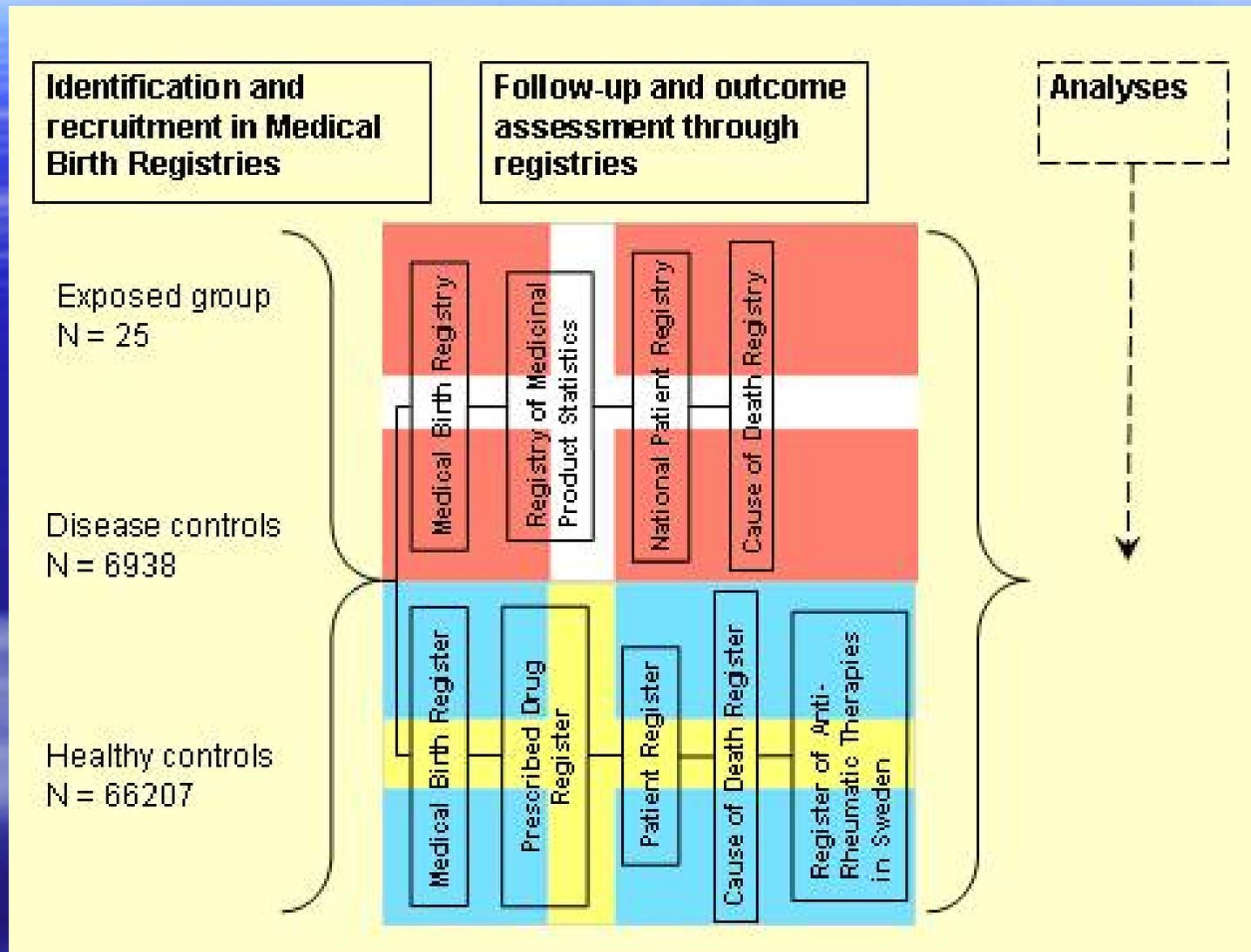
Infliximab and Infections in Infants



Specific aims

- Birth outcomes in newborns exposed to TNF-blockers
 - Gestational length
 - SGA
 - Apgar scores
 - Mode of delivery
 - Malformations
- Risk of infections in infants exposed to TNF-blockers
 - All infections
 - Specific infections
 - Antibiotic use

ICPE August 19, 2008 in Copenhagen



Results

	Exposed to Anti-TNF		Disease controls		Healthy controls	
	Number	(%)	Number	(%)	Number	(%)
Cesarean section	12	(48)	1643	(24)	66207	(16)
Preterm delivery*	6	(24)	546	(8)	3236	(5)
SGA delivery**	2	(11)	215	(3)	1436	(2)
Infant infections***	3	(12)	483	(9)	3899	(7)
Malformations	1	(4)	267	(4)	2295	(3)

* < 37 weeks

** < 2 SD from mean birth weight

*** Hospital admissions until 1 year of age

Conclusion

Only 25 infants born in Denmark or Sweden 1998-2006, had been exposed prenatally to anti-TNF agents. Data is too sparse to draw any conclusions concerning safety of anti-TNF during pregnancy to date



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