The Problem of Scientific Evidence in Prevention Programmes*:* the case of EU-Dap

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The paradigm of substance use prevention
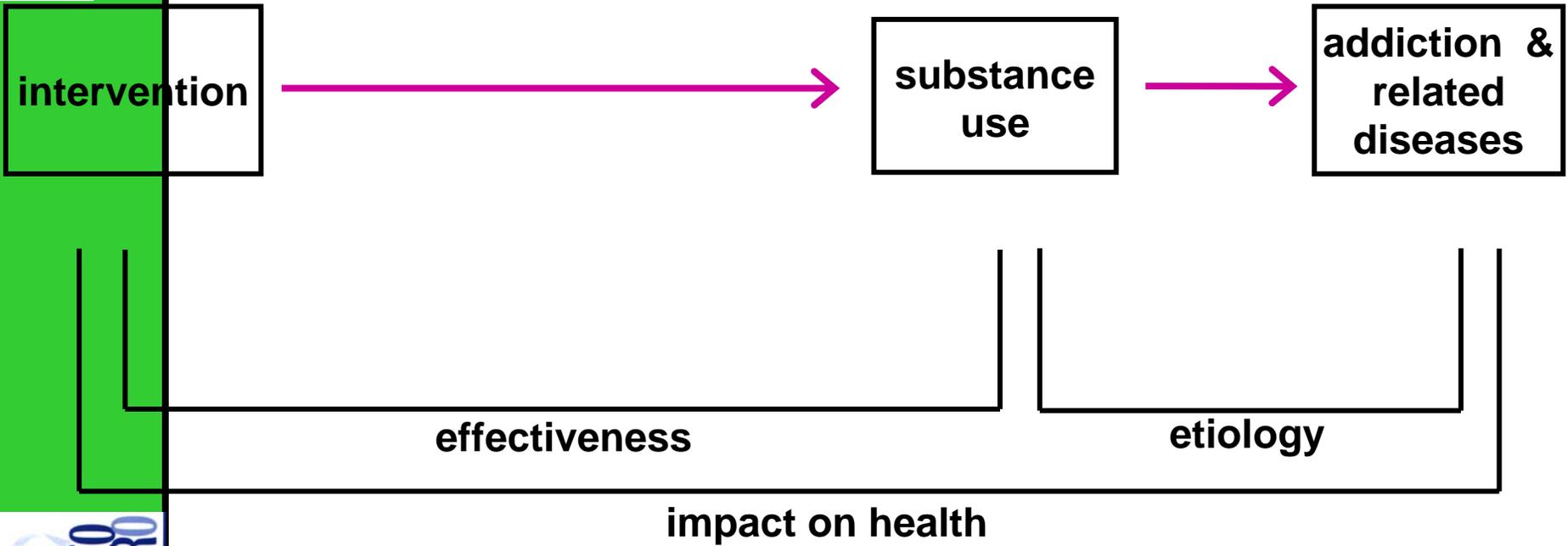
intervention → addiction & related diseases

impact on health

Primary prevention

- **interventions aimed to reduce a health problem by decreasing the exposure to the risk factor**

- **risk factor of addiction and related diseases is *substance use* (etiology)**

The paradigm of substance use prevention

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intervention  ──────────────────────────▶  substance  ──▶  addiction &
                                              use            related
                                                             diseases
```

effectiveness   etiology

impact on health

The effectiveness of primary prevention

- **Effectiveness**: the measure of the ability of an intervention to reach its **objectives at the level of health**

- **Outcome is the use of substances**

Effectiveness of primary prevention

- ***Community effectiveness*** depends on:
  - efficacy of the intervention
  - diagnostic accuracy
  - provider compliance
  - patient compliance
  - coverage

Tugwell, Bennett, Sackett, Haynes. J Chron Dis1985

Effectiveness of primary prevention

- For hypertention:
  - efficacy of the intervention   76%
  - diagnostic accuracy   95%
  - provider compliance   66%
  - patient compliance   65%
  - coverage   90%

  _____

  - community effectiveness
    (76%*95%*66%*65%*90%) =   28%

Tugwell, Bennett, Sackett, Haynes.
J Chron Dis1985

Dimentions of quality

Quality =

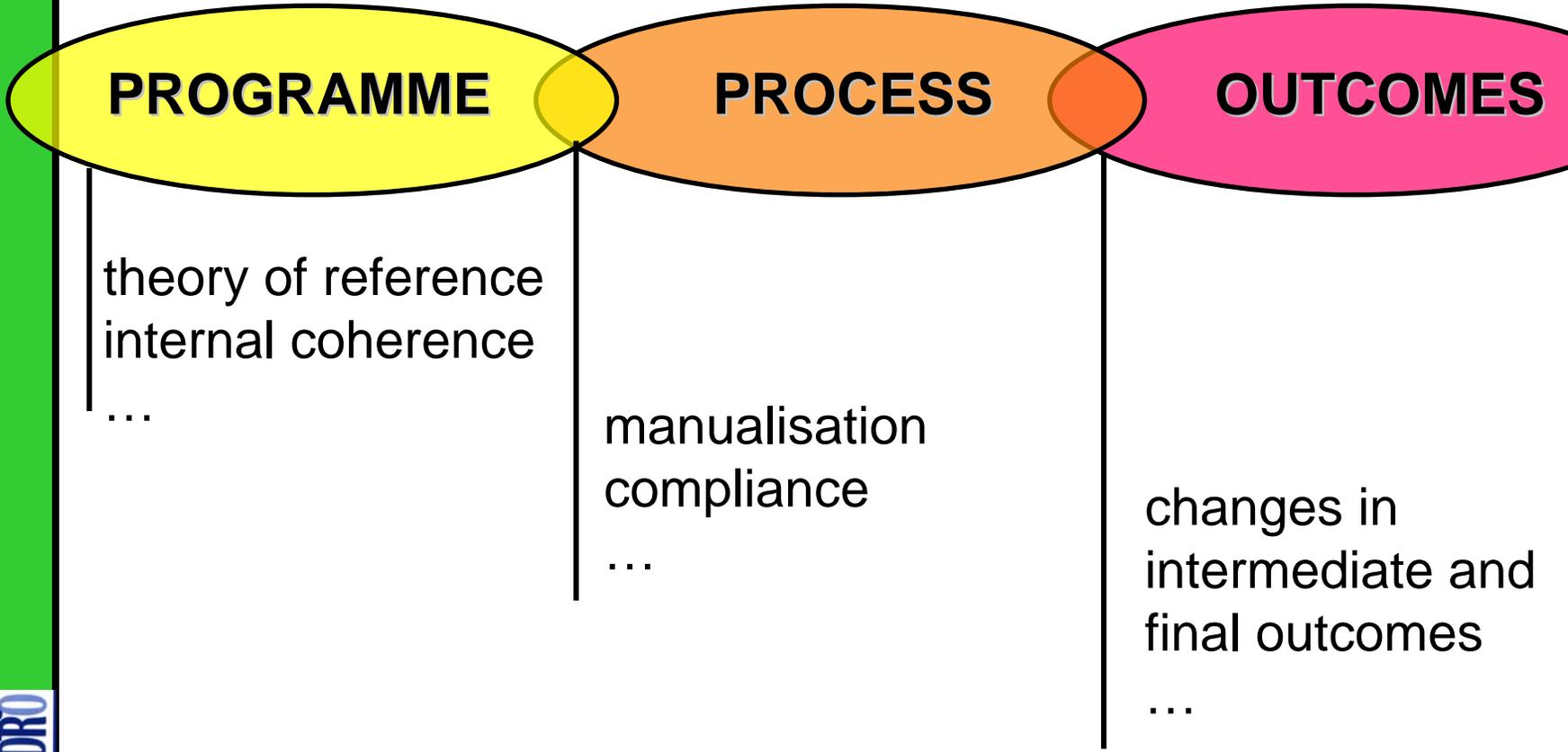| |
|---|
| Efficacy |
| Appropriateness |
| Effectiveness |
| Availability |
| Promptness |
| Continuity of care |
| Safety |
| Efficiency |
| Respect and attention |

Joint Committee on Health
Services Accreditation – 1998

Measurement of quality

PROGRAMME   **PROCESS**   **OUTCOMES**

theory of reference
internal coherence
…

manualisation
compliance
…

changes in
intermediate and
final outcomes
…

Can programme and process alone predict effectiveness?

Examples of iatrogenic effect

1. Hormone replacement therapy
2. Sudden Infant Death Syndrome
3. Life education
4. American National Youth Anti-drug Media Campaign

Hormone replacement therapy

- Women are protected towards CVD and osteoporosis

- This protection ends after menopause with the decrease of estrogens

- From '60ies women use HRT to preserve pre-menopausal protection

- Most part of scientific research (mainly animal experimentations and cohort studies) confirmed this theory

HRT: first observational studies

Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study
Stampfer, NEJM 1991

- RR for major CHD = 0.56 (0.40-0.80)
- RR for total mortality = 0.89 (0.78-1.00)
- RR for mortality from CVD = 0.72 (0.55-0.95)

HRT: first observational studies

Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence.
Stampfer, Prev Med 1991

"Overall, the bulk of the evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors. This benefit is consistent with the effect of estrogens on lipoprotein subfractions (decreasing low-density lipoprotein levels and elevating high-density lipoprotein levels)"

RR CHD= 0.56 (95% confidence interval 0.50-0.61)

HRT: first observational studies

Hormone replacement therapy and breast cancer mortality in Swedish women: results after adjustment for 'healthy drug-user' effect.

Yuen. Cancer Causes Control. 1993

- Cohort of 23,000 Swedish women, 12 years FU.

- SMR for breast cancer ranging from 0.71 to 0.81, (NS)

- prescribed estradiol, conjugated estrogens, or an estrogen-progestin combination RR 0.81

- estrogens, 0.68, respectively (NS)

Hrt: following confirmations

Postmenopausal hormone therapy and mortality.

Grodstein, N Engl J Med. 1997

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- Cohort study
- RR death =0.63 (0.56-0.70)

However, the apparent benefit decreased with long-term use (RR, 0.80; 0.67 to 0.96, after 10 or more years) because of an increase in mortality from breast cancer among long-term hormone users.

Hrt: following confirmations

Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT)

Sourander, Lancet 1998

- Cohort of 7944 women
- RR for CVD mortality in current users = 0.21 (0.08-0.59)
- RR in former users = 0.75 (0.41-1.37).
- Incidence of breast cancer = 1.8, 1.6, and 1.0 in never, former, and current users (p=0.242).

Hrt: last confermation

Postmenopausal Estrogen and Progestin Use and the Risk of Cardiovascular Disease

Grodstein Ann Int Medicine 2000

- 16 year results from the Nurses health study
- RR of CHD estrogen+progestin = 0.39 (0.19-0.78)
- RR of CHD estrogen alone = 0.60 (0.43-0.83).

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the
Women's Health Initiative
Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used

- 16608 postmenopausal women aged 50-79 years

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63

Decline in breast cancer since HRT study

Although the causal link hasn't been conclusively established, US researchers say there's been a remarkable decline in breast cancer rates since fewer women began taking hormone replacement therapy (HRT) to alleviate the symptoms of menopause

The overall incidence of breast cancer in the US declined 7% between 2002 and 2003, while the number of women aged 50–69 diagnosed with estrogen receptor positive (ER-positive) breast cancer declined 12% over the same period, when millions of women stopped taking HRT after the release of a July 2002 Women's Health Initiative study indicating HRT bore more risks than benefits.

Some 14 000 fewer women were diagnosed with breast cancer in 2003 than in 2002, when an estimated 203 500 cases were diagnosed, researchers at the University of Texas MC Anderson Cancer Center told the 29th annual San Antonio Breast Cancer Symposium last month.

Kondro, CMAJ Feb 2007

SPECIAL REPORT

The Decrease in Breast-Cancer Incidence
## ...d States
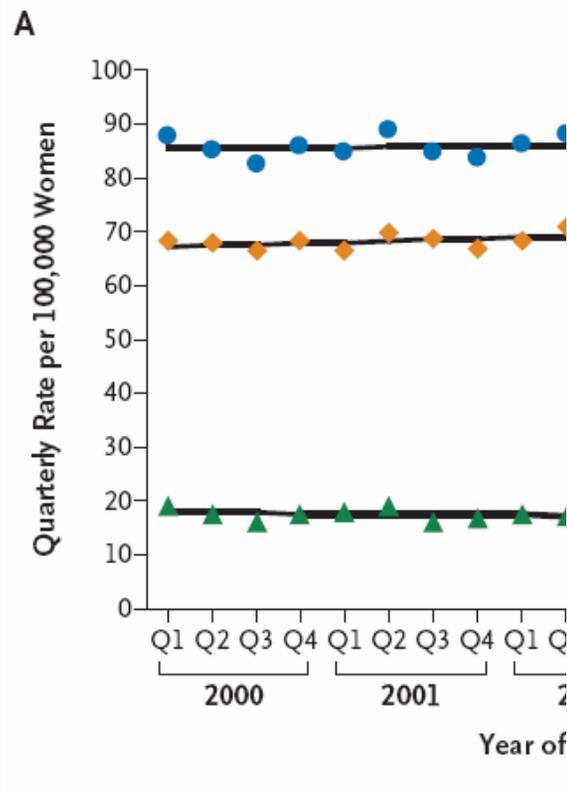
Ph.D., Nadia Howlader, M.S.,

age-adjusted incidence was 8.6% (95% confidence interval [CI], 6.8 to 10.4). The decrease was evident only in women who were 50 years of age or older and was more evident in cancers that were estrogen-receptor–positive than in those that were estrogen-receptor–negative. The decrease in breast-cancer incidence seems to be temporally related to the first report of the Women's Health Initiative and the ensuing drop in the use of hormone-replacement therapy among postmenopausal women in the United States. The contributions

Sudden Infant Death Syndrome

- during '80ies SIDS was responsible for 3-4 deaths per 1000 born

- Prone position during sleep has been recommended from 1943 to 1988

- On the basis of the theoretical risk of suffocation caused by regurgiotation, vomit, cough, colics …

- First Guidelines recommending supine position have been published in 1992

SIDS
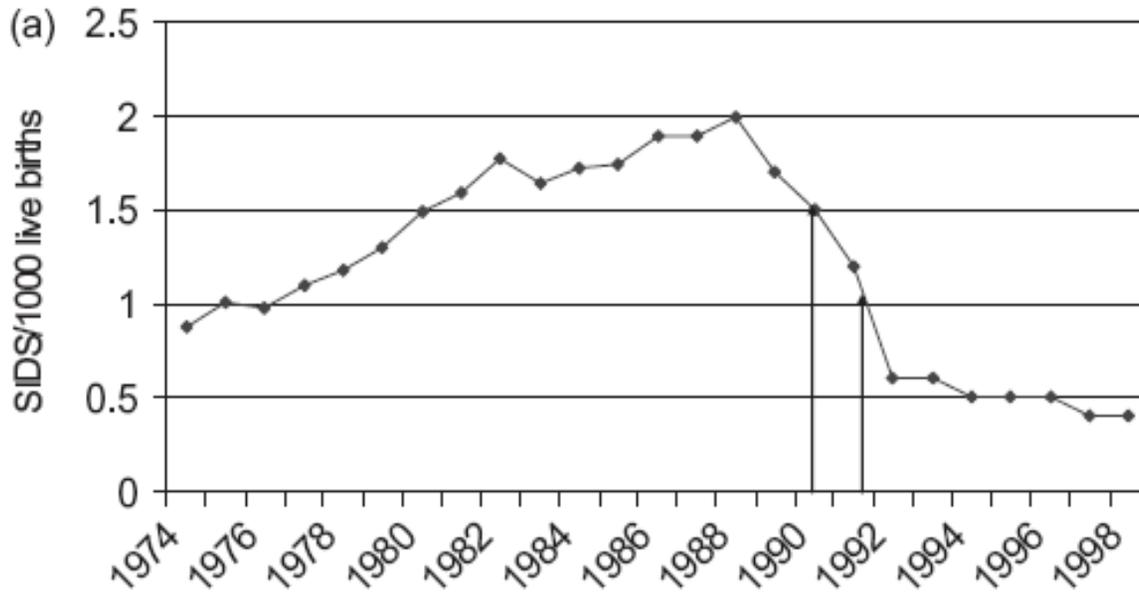
SIDS mortality
(a) Sweden
(b) AU, NZ, USA
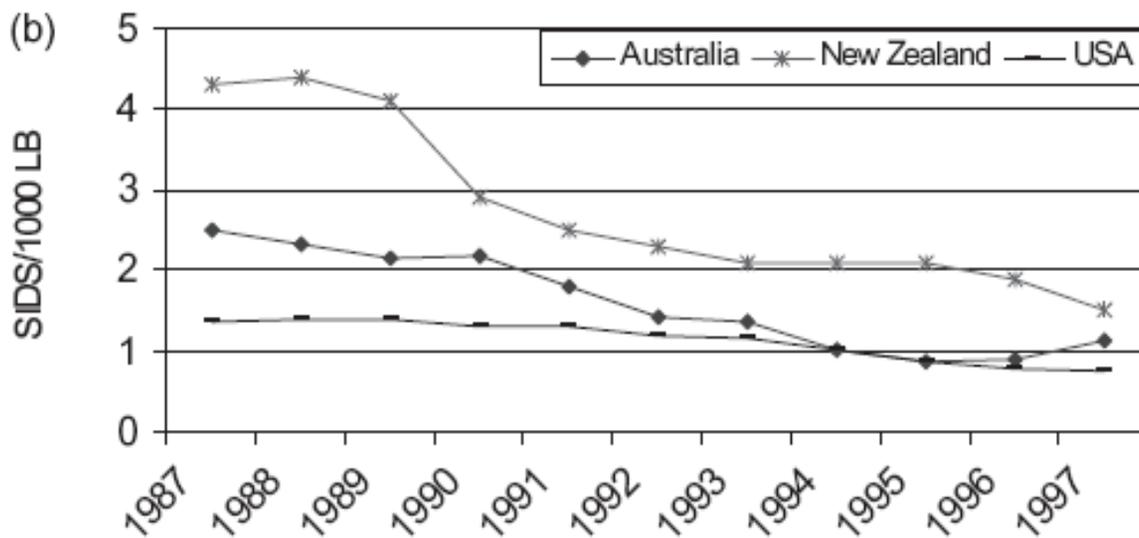
Jilbert, IJE 2005
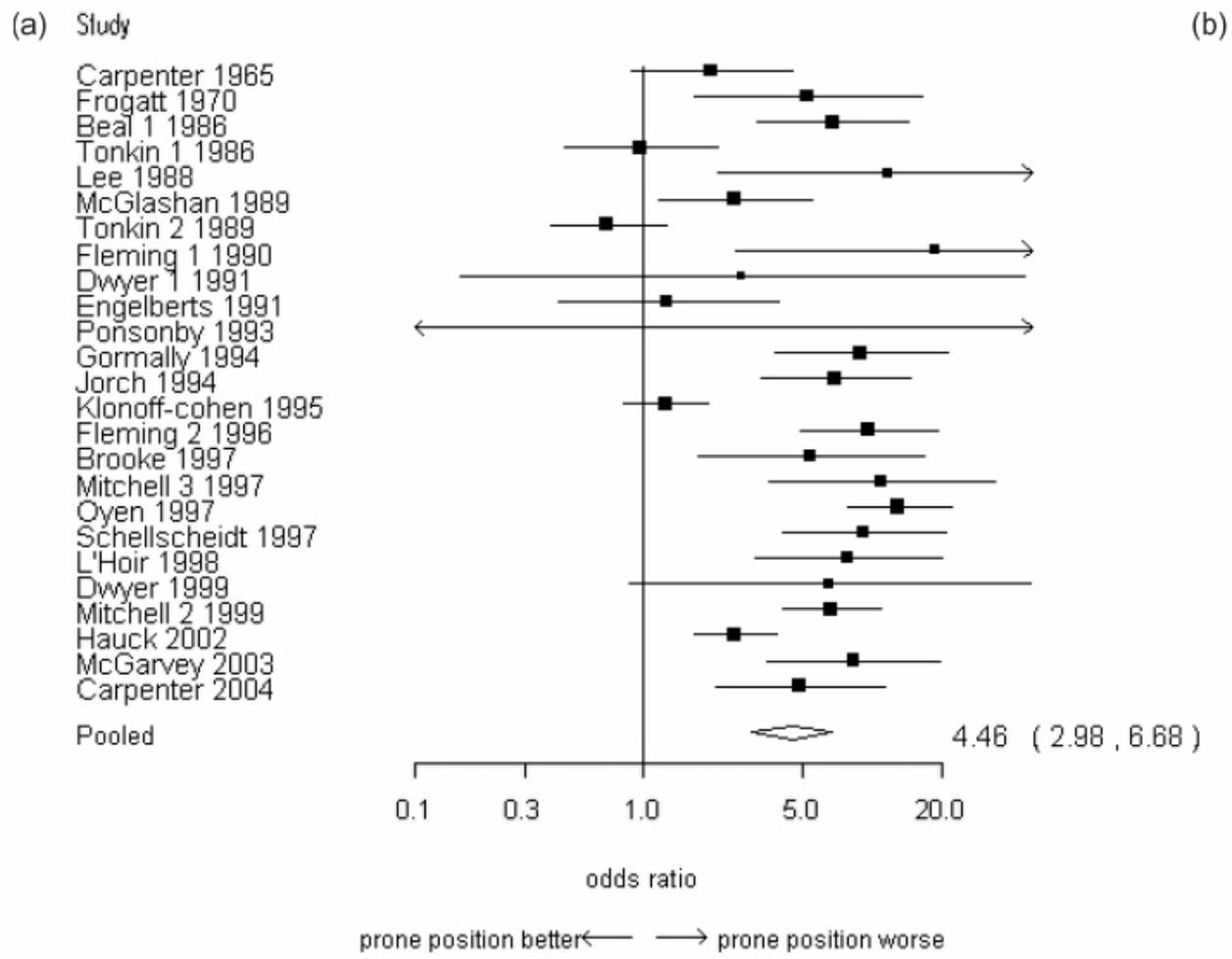
SIDS

Systematic review: RR of death prone vs supine position

SIDS: cumulative meta-analysis

Jilbert, IJE 2005
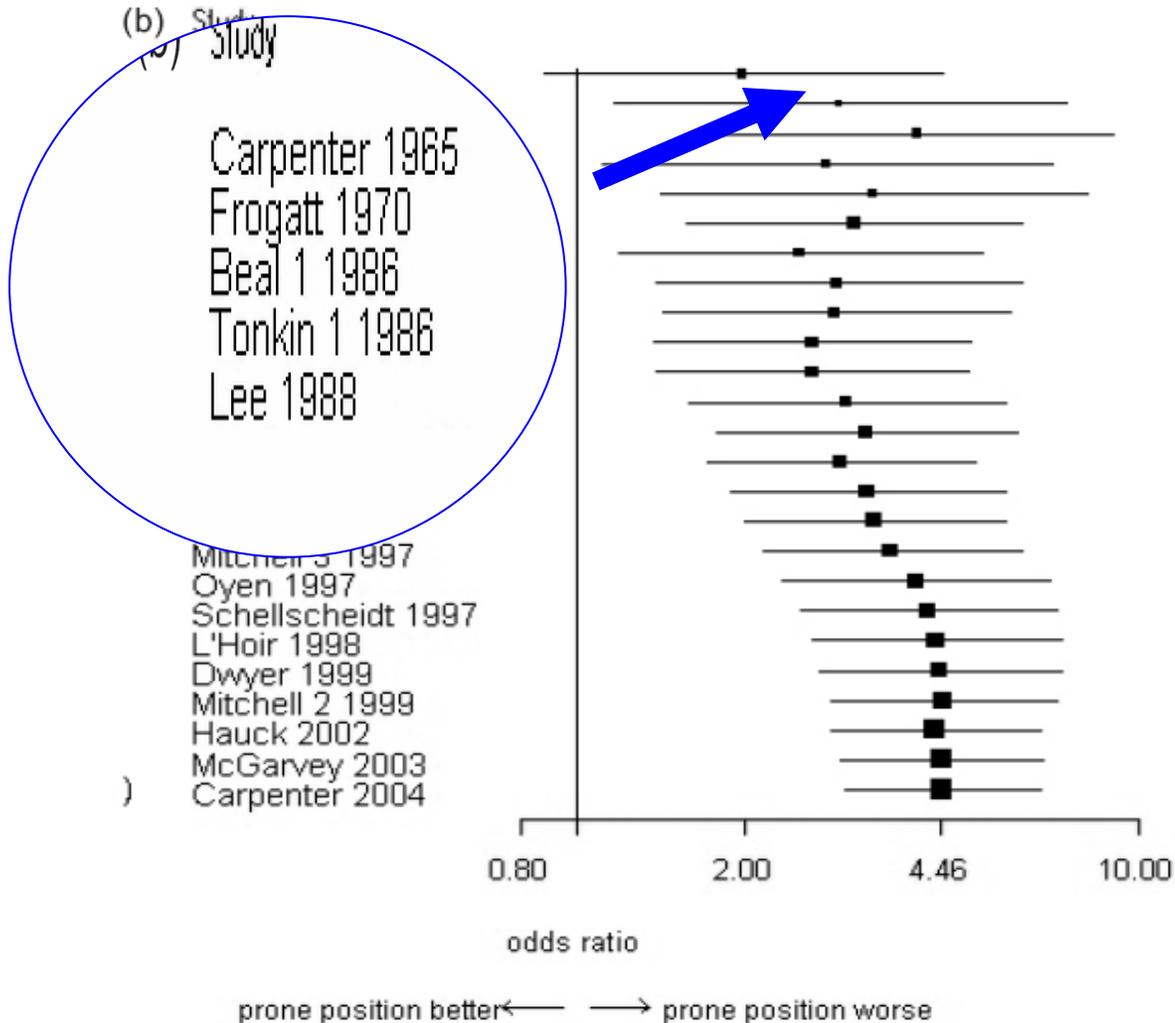
SIDS

- Jilbert suggests that the delay in the transfer of information was due to the higher attraction of the theoretical mechanisms on death in relation to experimental evidence

- From 1970 to 1992 **10000 deaths** among newborns in USA and **50000** in Europe could be prevented if guidelines have been published before

Life education

A school-based program in Australia:
- Cigarettes RR=1.6
- Alcohol RR=1.4
- Other substances RR=1.4

When the data are extrapolated to the state-wide ... estimates, ... of all smoking among year 6 schoolchildren,

25% of girls' and 19% of boys' smoking could be attributed to participation in Life Education

as could 22% of all boys' recent drinking

The findings suggest that intervention programmes should be thoroughly evaluated prior to widespread implementation…

Hawthorne, Addiction 1995

American National Youth Anti-drug Media Campaign

- planned by the National Drug Control Policy (ONDCP)
- funded in 1997 by the United States Congress with $1 billion dollars
- main objective: "to educate and enable America's youth to reject illegal drugs as well as alcohol and tobacco"
- alcohol and tobacco were omitted from the main focus of the campaign
- focused mainly on minimizing illegal drug use among young adolescents who have not yet become "regular" users of illegal substances
- televised antidrug public service announcements (PSAs) broadcasted 1998-2004

American National Youth Anti-drug Media Campaign

- Evaluation provides no evidence of positive effect in relation to teen drug use, and shows some indications of a negative impact.
- Some intermediate outcomes (parents talking with children about drugs, and doing fun activities with their children) showed positive results.
- Other (parents' monitoring of their children's behaviours) were not shown to be affected

- the past month use of marijuana appeared significantly increased by 2.5% among 14-18 years (Orwin 2006).
- post-2002 results: statistically significant increase in rates of marijuana use initiation among youth who were prior nonusers (2000 to 2004 change 2.1%)

Preliminary conclusions (I)

Because professionals sometimes do more harm than good when they intervene in the lives of other people, their policies and practices should be informed by rigorous, transparent, up-to-date evaluations.

Preliminary conclusions (II)

- The quality of structure and process cannot predict effectiveness

- Observational studies as well as qualitative research are not able to yield *unbiased estimations of effects of prevention programmes*

- *Results from experimental studies (RCTs)* have to be considered the *most important quality criteria* of prevention programmes, whenever possible

Preliminary conclusions (III)

- When experimental studies are not possible, as for:

  - mass media campaigns

  - legislation changes

- the rigorous rules of *quasi-experimental studies* have to be applied (Campbell 1969)

Systematic review: School-based prevention for illicit drugs' use

- *Systematic review* is a methodology developed by the *Evidence Based Medicine* to summarise the results of scientific studies

- The *Cochrane Collaboration* is the international no-profit network aimed at developing systematic reviews on effectiveness of health technologies using standardised methodologies

- Cochrane Library (www.cochrane.org)

Methods

Literature search and inclusion criteria

- RCTs and CPS (Controlled Prospective Studies)

- databases searched (from beginning to feb 2004)

  - Medline & Embase

  - ERIC, Sociological Abstracts, Psychinfo

  - Cochrane databases

- To discover unpublished researches/results, research teams, and 18 authors of studies were contacted

Flow-chart of considered studies

9657 reports identified

→ 7441 reports excluded

2216 abstracts evaluated

→ 1538 reports excluded

678 full texts obtained

→ **613 reports excluded**
374: methodological reasons
128: reviews
76: community programs
35: alcohol focused programs

65 reports prov. incl.(40 RCTs)

→ 24 reports excluded (21 RCTs)

41 reports included (29 RCTs)

→ 14 RCTs no useful data

15 RCTs with useful data

Results
Included studies

- 29 studies (41 reports) were included
- 14 did not present data for inclusion in the meta-analyses (limited reporting from statistical models)
- 18 studies were of 6th and 7th grade students

- 18 studies presented a post-test assessment;
- 13 provided data at 1 year follow-up.
- Few studies provided data for longer periods

- 28/29 were conducted in the USA (1 RCT in the UK)

Methods

Data collection and extraction

- For the 29 RCTs included, interventions and control arms were classified as:

  - *skills focused*, aimed to enhance students' abilities in generic, refusal, and safety skills

  - *affective focused*, aimed to modify inner qualities (personality traits such as self-esteem and self-efficacy, and motivational aspects such as the intention to use drugs)

  - *knowledge focused programs*, aimed to enhance knowledge of and the effects, and consequences of drug use

  - *usual curricula*

Results
Skills versus usual curricula

The only comparison showing significant results are skills vs usual curricula

Review: School-based prevention for illicit drugs' use.
Comparison: 02 skills vs usual curricula
Outcome: 07 drug use

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Ringwalt 1991	65/685	77/585		52.56	0.72 [0.53, 0.98]
Snow 1992	63/575	63/526		47.44	0.91 [0.66, 1.27]
Total (95% CI)	1260	1111		100.00	0.81 [0.64, 1.02]

Total events: 128 (Treatment), 140 (Control)

Test for heterogeneity: Chi² = 1.06, df = 1 (P = 0.30), I² = 6.0%

Test for overall effect: Z = 1.80 (P = 0.07)

0.2   0.5   1   2   5

Favours treatment   Favours control

Results
Skills versus usual curricula

Review: School-based prevention for illicit drugs' use. (Vs first published 2/2005
Comparison: 02 skills vs usual curricula
Outcome: 13 hard drugs use

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Sussman 2002	9/200	15/176		61.43	0.53 [0.24, 1.18]
Furr-Holden 2004	5/192	13/178		38.57	0.36 [0.13, 0.98]
Total (95% CI)	392	354		100.00	0.45 [0.24, 0.85]

Total events: 14 (Treatment), 28 (Control)
Test for heterogeneity: Chi² = 0.36, df = 1 (P = 0.55), I² = 0
Test for overall effect: Z = 2.47 (P = 0.0

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         0.1   0.2    0.5   1    2     5    10
         Favours treatment    Favours contro
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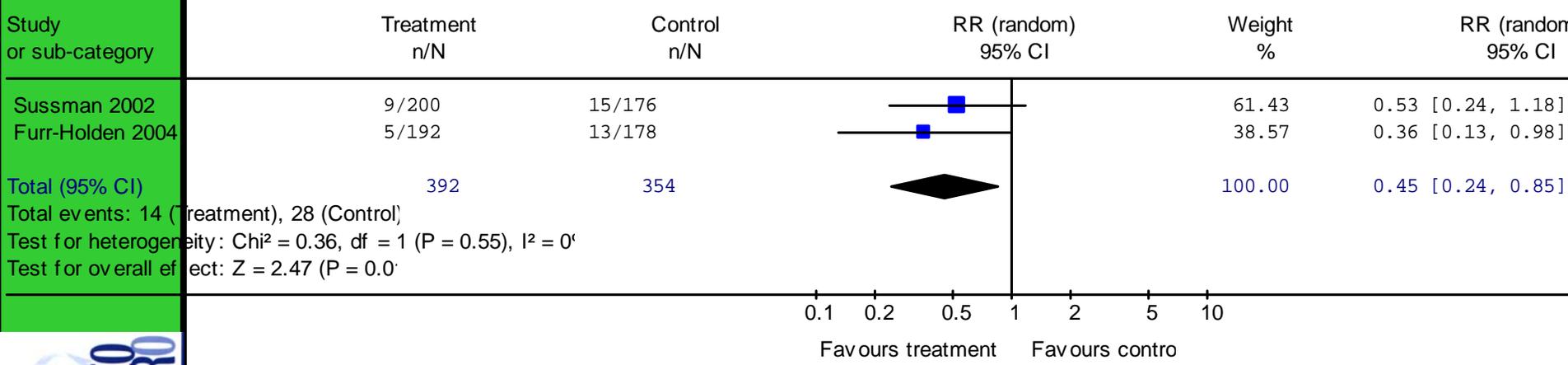
Results
Skills versus usual curricula

Review: School-based prevention for illicit drugs' use. (Vs first published 2/2005

Comparison: 02 skills vs usual curricula

Outcome: 08 marijuana use (all studies)

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Sussman 2002	46/199	44/172		10.09	0.90 [0.63, 1.29]
Botvin 1990	147/1128	160/1142		28.69	0.93 [0.76, 1.15]
Ellickson 2003	332/2553	293/1723		55.38	0.76 [0.66, 0.88]
Furr-Holden 2004	25/192	34/178		5.85	0.68 [0.42, 1.10]
Total (95% CI)	4072	3215		100.00	0.82 [0.73, 0.92]

Total events: 550 (Treatment), 531 (Control)

Test for heterogeneity: Chi² = 3.15, df = 3 (P = 0.37), I² = 4.8%

Test for overall effect: Z = 3.43 (P = 0.0006

0.2 0.5 1 2 5

Favours treatment   Favours contro

Results
Skills versus usual curricula

- Skills based intervention reduced
  - drug use (RR=0.81 => -19%)
  - hard drug use (RR=0.45 => -55%)
  - marijuana use (RR=0.82 => -18%)

- Improvement in intermediate variables
  - drug knowledge (WMD=2.60; CI95%: 1.17, 4.03)
  - decision making skills (SMD=0.78; CI95%: 0.46, 1.09)
  - peer pressure resistance (RR=2.05; CI95%: 1.24, 3.42)
  - self-esteem (SMD= 0.22; CI95%: 0.03, 0.40)

Other results

- Other interventions
  - No significant differences were found comparing other programmes with usual curricula
  - neither in comparisons between programmes

- peer involvement
  - no final outcomes have been used by studies comparing peer involvement vs control

General considerations

- The wide variability of indicators, scales and scores employed, and the limited reporting of data make *results very heterogeneous*

- The *quality* of research is *generally low* (out of 50 selected RCTs, only 29 were included)

- There is a major concern on *generalisability*: 28/29 RCTs included were conducted in the USA

- Authors stated for a need of *further corroboration* of results by well designed, long term follow-up, cluster-randomised trials, especially in countries other than the USA

The EU-Drug Abuse Prevention project

- ***EU-Dap*** is an experimental study
  - involving 9 centers in 7 European Countries
  - funded by European Commission (*Public Health Program*)
  - supported by EMCDDA
- for the evaluation of a school program (called "***Unplugged***")
  - to prevent tobacco, alcohol and drugs onset
  - especially conceived by an internal expert group

The program "Unplugged"

- based on a ***comprehensive social influence approach***
  - including the following components:
    - social skills
    - personal skills
    - knowledge
    - normative education

- delivered by the class teachers, trained with a 3-days training course

- composed by 12 one-hour units delivered weekly from October 2004 to January 2005

Design of the evaluation

- EU-Dap is a ***Cluster randomised controlled trial***

  - schools were randomised
  - students were the unit of analysis

- The schools to be included were selected by chance among all schools of the centre area

- A stratified randomisation was carried out to ensure a balanced sample according to ***social status***

- More details published in PM - Faggiano 2006

Questionnaire

- Self completed ***anonymous*** questionnaire on use of substances, attitudes, knowledge…

  - most items retrieved from ***EDDRA data bank***

  - identical for all countries

- Linkage between pre- and post-test by a ***self generated anonymous code*** based on fixed data (some letters from name of parents, date of birth..)

- the ***reliability*** was tested in a pilot study (Galanti 2006)
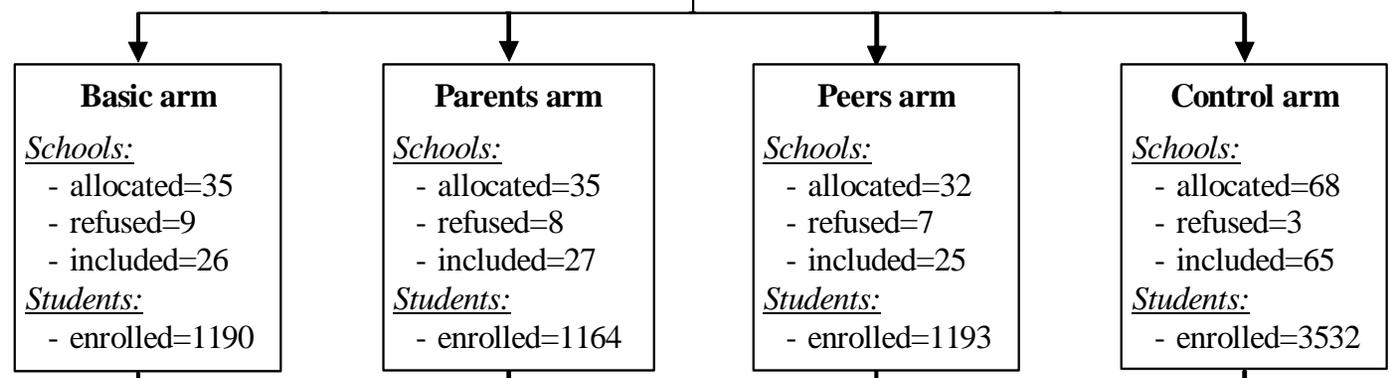
Enrollment

- 7079 students were enrolled at the ***baseline survey*** (November 2004)

- 1° follow-up survey - May 2005:

  - 6604 participated the program
  - 6370 out of 7079 (91.5%) baseline questionnaires matched to the corresponding follow-up questionnaire

- 2° follow-up survey - May 2006:

  - 5812 participated
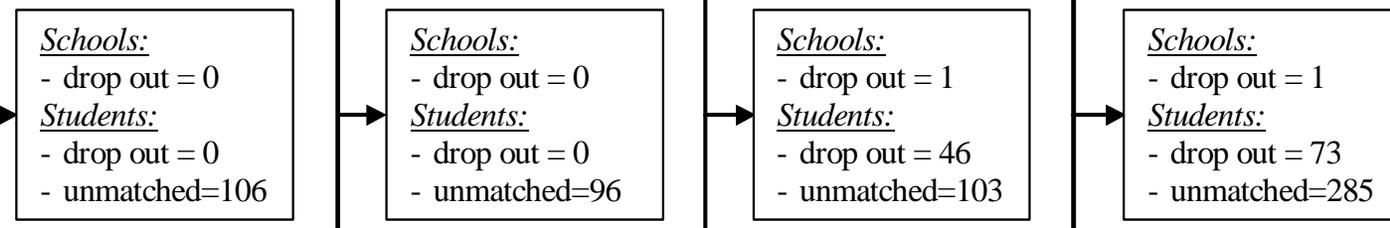 - 5541 out of 7079 (81.4%) baseline questionnaires matched

Enrollment

Schools
assessed
n=344

Schools
excluded
n=174

Schools
randomised
n=170

Allocation

Basic arm

Schools:
 - allocated=35
 - refused=9
 - included=26
Students:
 - enrolled=1190

Parents arm

Schools:
 - allocated=35
 - refused=8
 - included=27
Students:
 - enrolled=1164

Peers arm

Schools:
 - allocated=32
 - refused=7
 - included=25
Students:
 - enrolled=1193

Control arm

Schools:
 - allocated=68
 - refused=3
 - included=65
Students:
 - enrolled=3532

Follow up

Schools:
 - drop out = 0
Students:
 - drop out = 0
 - unmatched=106

Schools:
 - drop out = 0
Students:
 - drop out = 0
 - unmatched=96

Schools:
 - drop out = 1
Students:
 - drop out = 46
 - unmatched=103

Schools:
 - drop out = 1
Students:
 - drop out = 73
 - unmatched=285

Analysis

Schools:
 - analyzed=26
Students:
 - analyzed=1084

Schools:
 - analyzed=27
Students:
 - analyzed=1068

Schools:
 - analyzed=24
Students:
 - analyzed=1044

Schools:
 - analyzed=64
Students:
 - analyzed=3174

Characteritics of the analysis sample

	Study Arm					
	Controls (N=3297)		Pooled interventions (N=3307)		Total population (N=6604)	
	n	%	n	%	n	%
Gender						
boys	1629	51.3	1695	53.0	3324	52.2
girls	1538	48.5	1497	46.8	3035	47.6
missing	7	0.2	4	0.1	11	0.2
Age						
12 years	1043	32.9	998	31.2	2041	32.0
13 years	851	26.8	1135	35.5	1986	31.2
14 years	1280	40.3	1063	33.3	2343	36.8

Characteritics of the analysis sample

Centres	Controls (N=3297)		Pooled interventions (N=3307)		Total population (N=6604)	
	n	%	n	%	n	%
Italy - Turin	859	27.1	634	19.8	1493	23.4
Spain - Bilbao	212	6.7	159	5.0	371	5.8
Germany - Kiel	203	6.4	358	11.2	561	8.8
Belgium - Gent	288	9.1	347	10.9	635	10.0
Sweden - Stockholm	426	13.4	501	15.7	927	14.5
Greece - Thessaloniki	322	10.1	368	11.5	690	10.8
Austria - Wien	433	13.6	283	8.8	716	11.2
Italy - Novara	209	6.6	270	8.4	479	7.5
Italy - Aquila	222	7.0	276	8.6	498	7.8

Study Arm

Outcomes measures

1. ***Any smoking***= at least one sigarette in last 30 days
2. ***Frequent Smoking***= at least 6 times in last 30d
3. ***Daily smoking***= at least 20 times in last 30d
4. ***Any drukenness***= at least once in last 30d
5. ***Frequent drunkeness***= at least 3 times in last 30d
6. ***Any cannabis***= at least once in last 30d
7. ***Frequent cannabis***= at least 3 times in last 30d
8. ***Any drugs***= at least once of any illicit drug in last 30d

Conclusions

- *Any primary prevention program needs a rigorous evaluation of effectiveness*
- Rigorous evaluation means randomised experimentation
- Rigorous experimental studies to evaluate programs aimed at drug abuse prevention are very difficult, but anyway feasible, at the European level

The EU-Dap Study Group

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www.eudap.net