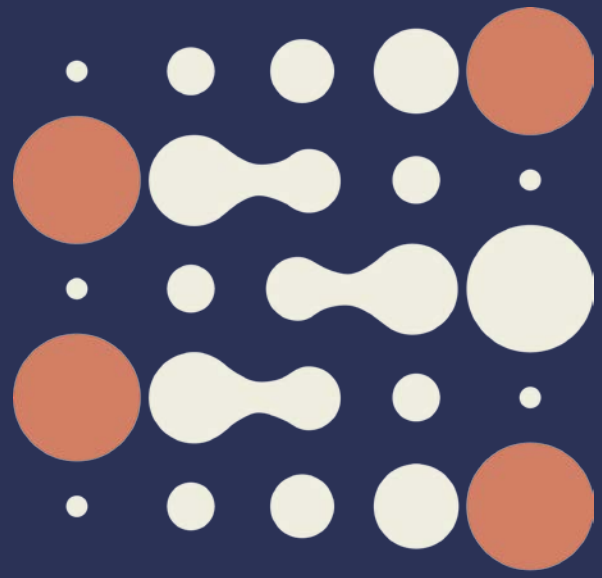
Opportunities and challenges of using epidemiological studies in health risk assessment from an IARC perspective

Joachim Schüz
Head, Environment and Lifestyle Epidemiology Branch



International Agency for Research on Cancer
World Health Organization

International Conference:
Using Epidemiological Studies in Health Risk Assessments: Relevance, Reliability and Causality
Berlin, 9-10 November 2023

Research areas

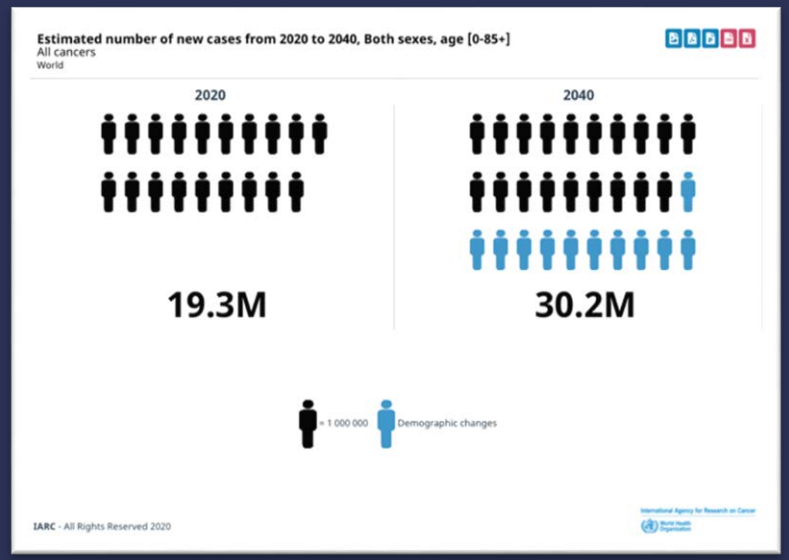
IARC Monographs Program and Handbooks on Cancer Prevention

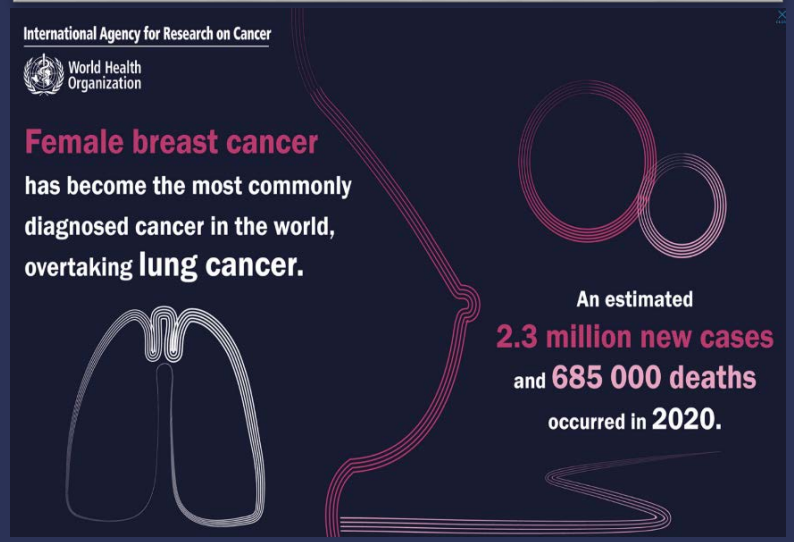
IARC Recommendations on Cancer Prevention
- World Code against Cancer Framework
- Europe (4th edition 2012), Latin America & the Caribbean (2023)

IARC Output based on reviews and health risk assessments
- e.g. Attributable fractions of cancer in France 2015
- e.g. Thyroid screening after nuclear accidents

Research activities with critical appraisal of results
- Research consortia
- Multinational or national fieldwork studies

Cancer: the global burden





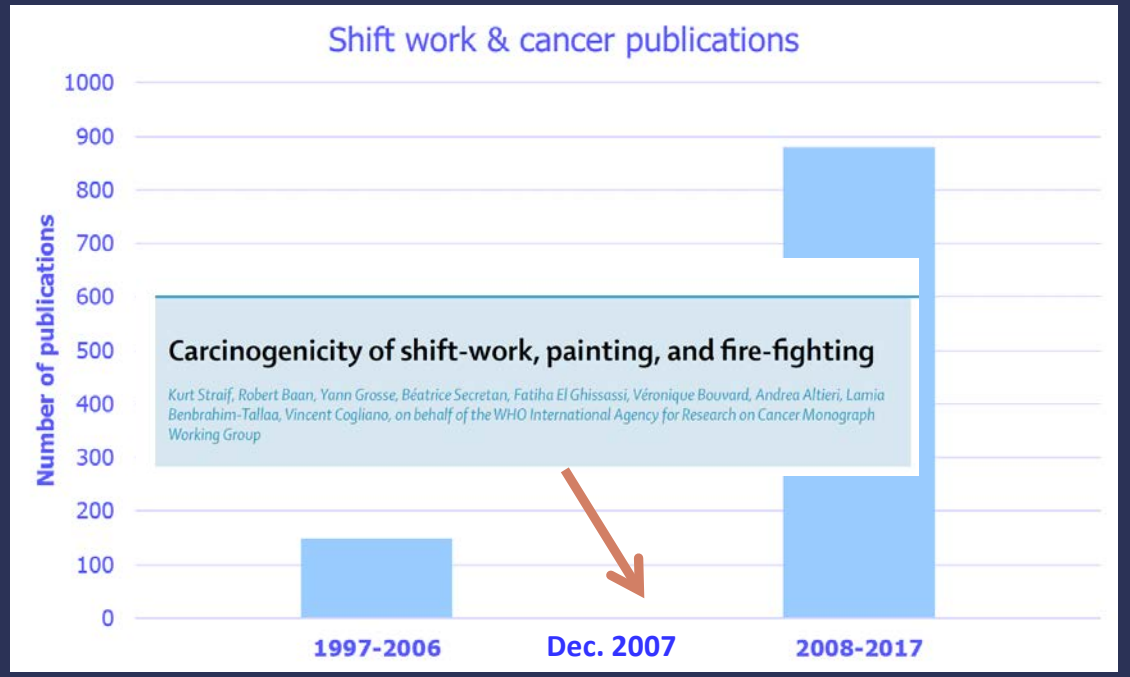
- Epidemiologic transition → rising global burden
  - Changing demographics
  - Shift in carcinogenic exposures to LMICs
- Prevention is the single most effective response to these challenges
- The first step in cancer prevention is to identify **causes of human cancer (*IARC Monographs*)** and **what prevents cancer (*IARC Handbooks*)**

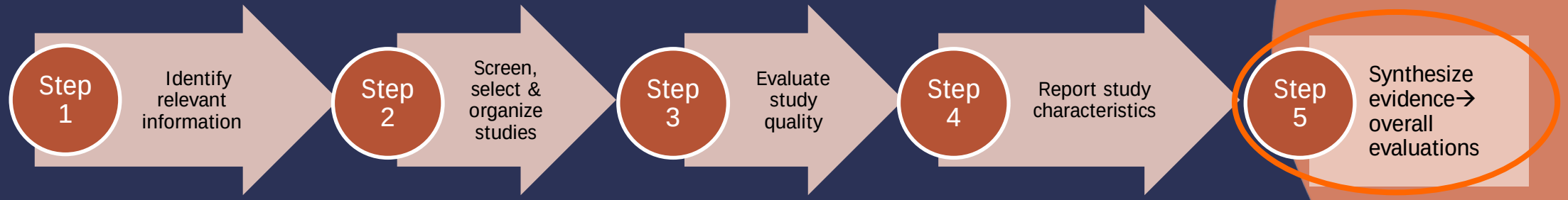
http://monographs.iarc.fr

http://handbooks.iarc.fr

Monographs : Dual role in global cancer research

- Evaluate results of latest scientific research in different disciplines
- Stimulate new research to fill identified gaps and to further develop findings





Synthesis: Categorize each line of evidence using defined terms

Cancer in humans

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
- *Evidence suggesting lack of carcinogenicity*

Cancer in experimental animals

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
- *Evidence suggesting lack of carcinogenicity*

Mechanistic evidence

- *Strong evidence*
  - *Mechanistic class*
  - *Key characteristics*
  - *Mechanism not relevant*
- *Limited evidence*
- *Inadequate evidence*

Overall evaluations: Integrate findings from 3 evidence streams

Overall evaluation

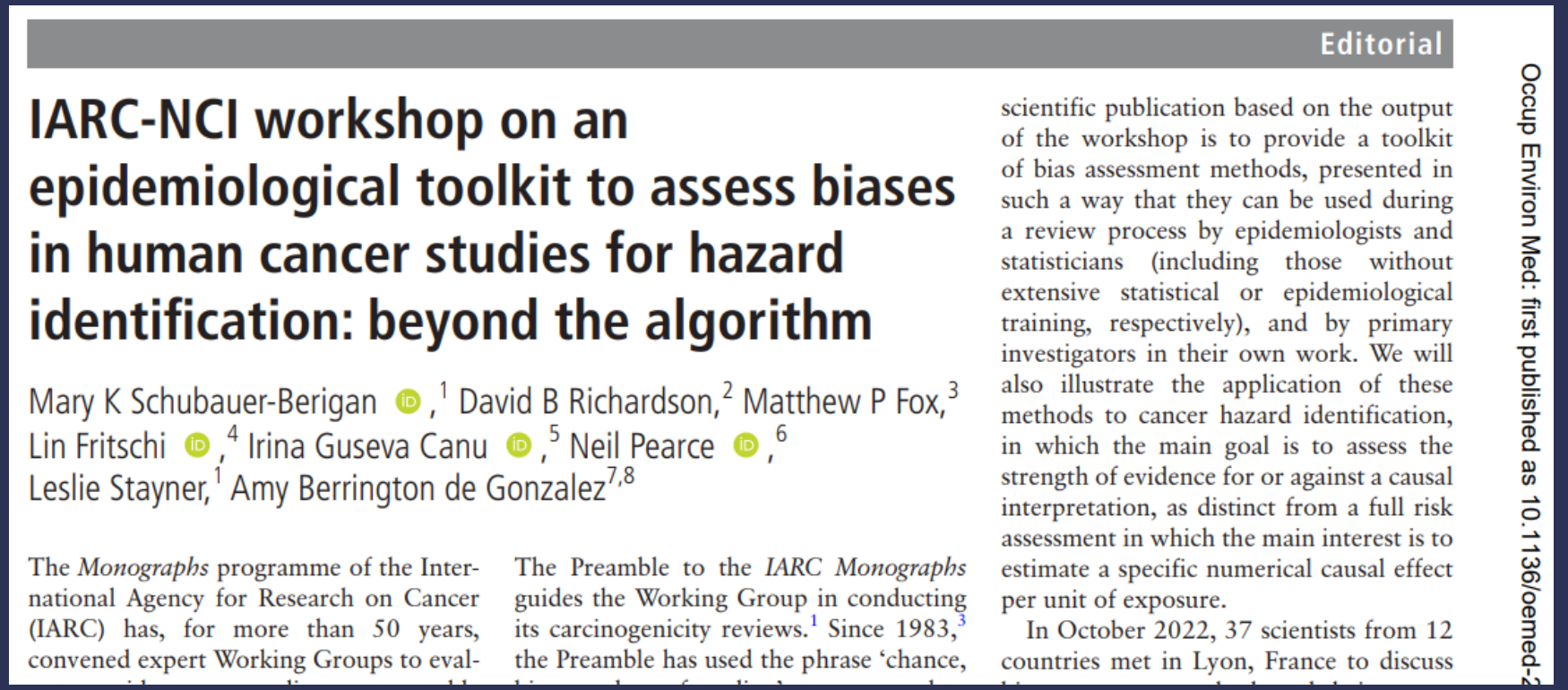
- Group 1 *Carcinogenic to humans (n=127)*
- Group 2A *Probably carcinogenic to humans (n=95)*
- Group 2B *Possibly carcinogenic to humans (n= 323)*
- Group 3 *Not classifiable as to its carcinogenicity to humans (n=500)*

Overall classifications

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong (experimental systems)	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Scientific Workshop & IARC Scientific Publication

What's next?



Editorial

IARC-NCI workshop on an epidemiological toolkit to assess biases in human cancer studies for hazard identification: beyond the algorithm

Mary K Schubauer-Berigan [1], David B Richardson,[2] Matthew P Fox,[3] Lin Fritschi [4], Irina Guseva Canu [5], Neil Pearce [6], Leslie Stayner,[1] Amy Berrington de Gonzalez[7,8]

The *Monographs* programme of the International Agency for Research on Cancer (IARC) has, for more than 50 years, convened expert Working Groups to eval-

The Preamble to the *IARC Monographs* guides the Working Group in conducting its carcinogenicity reviews.[1] Since 1983,[3] the Preamble has used the phrase 'chance,

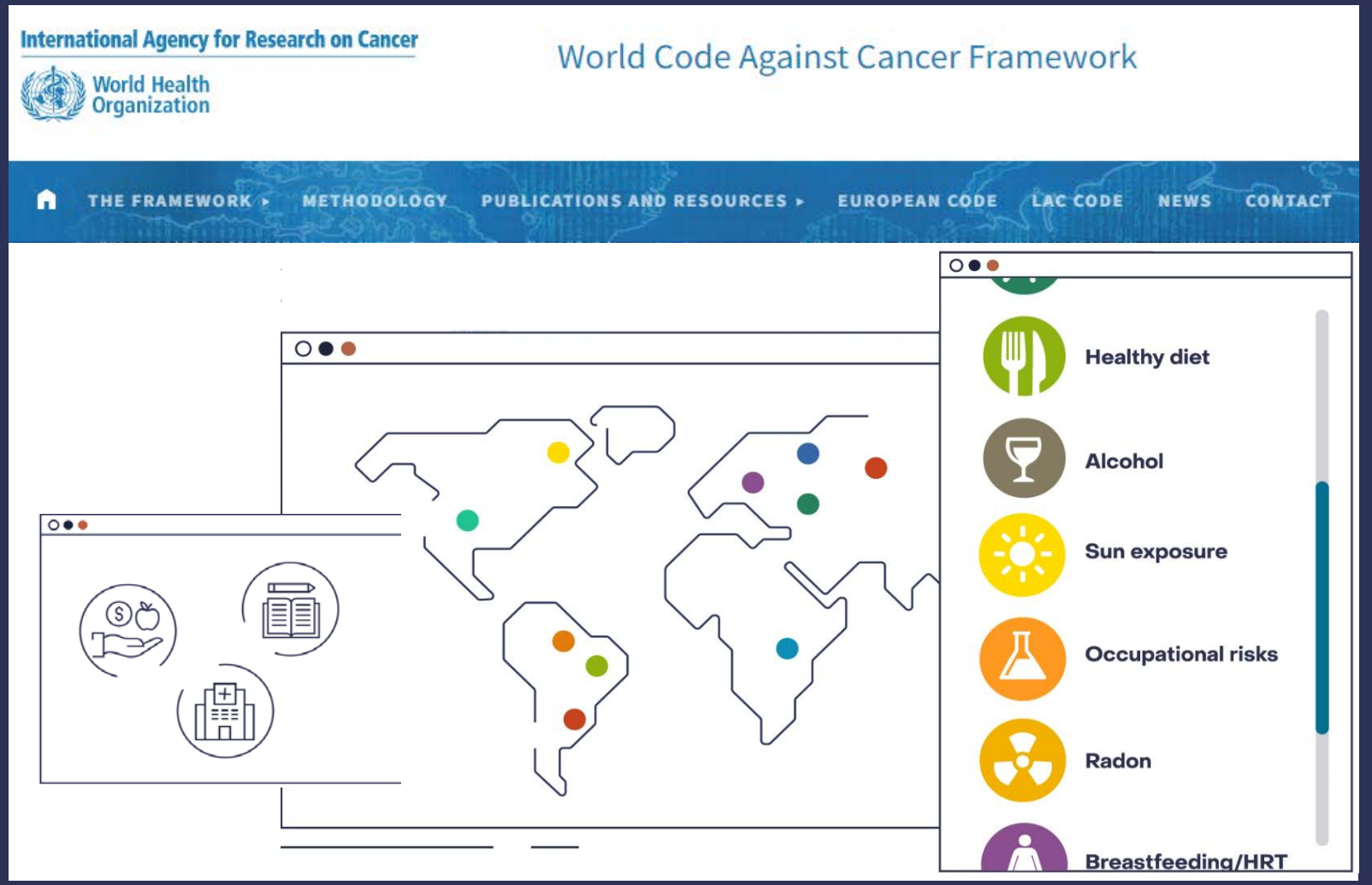
scientific publication based on the output of the workshop is to provide a toolkit of bias assessment methods, presented in such a way that they can be used during a review process by epidemiologists and statisticians (including those without extensive statistical or epidemiological training, respectively), and by primary investigators in their own work. We will also illustrate the application of these methods to cancer hazard identification, in which the main goal is to assess the strength of evidence for or against a causal interpretation, as distinct from a full risk assessment in which the main interest is to estimate a specific numerical causal effect per unit of exposure.

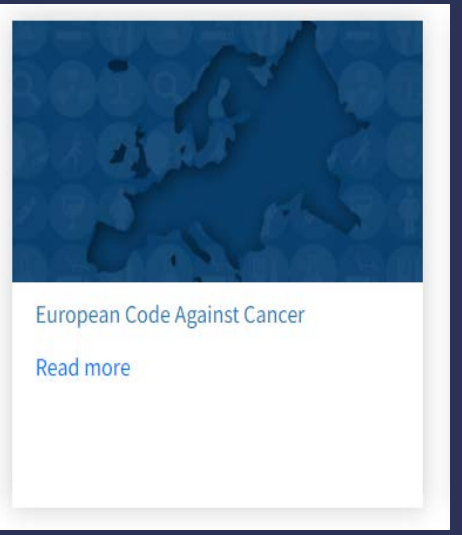
In October 2022, 37 scientists from 12 countries met in Lyon, France to discuss

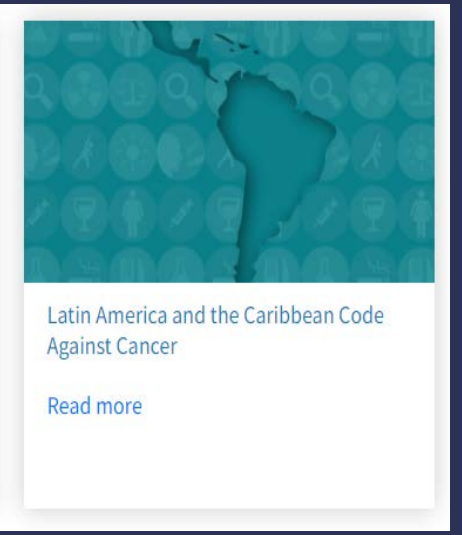
Occup Environ Med: first published as 10.1136/oemed-2

IARC Scientific Publication in Spring 2024

Update of the European Code against Cancer under the World Code Against Cancer Framework







Methodology: decision-making tree

Starting

Recommendation from a previous Code to be updated, or new recommendation (takes into account other Regional Codes for guidance)

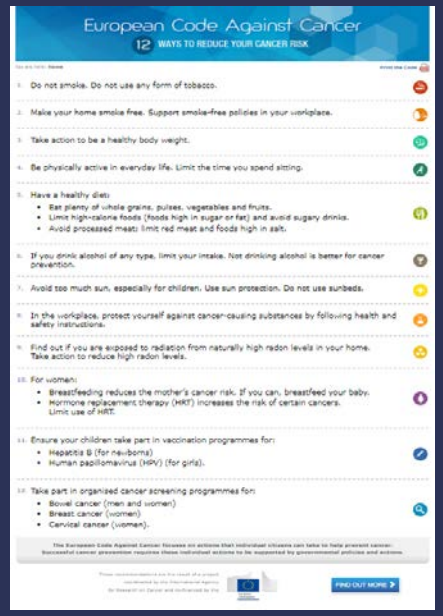
Criterion 1: Confidence in the evidence to keep, modify or add a recommendation that is relevant for the region or a large sub-region

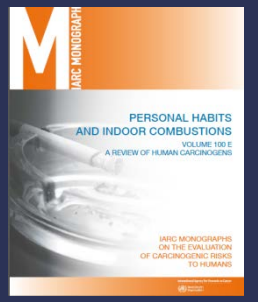
Criterion 2: Suitability and acceptability for a broad target population of the general public in the EU

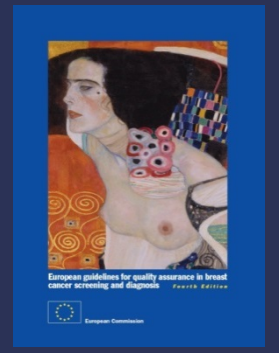
Criterion 3: Intelligibility of the formulation of the recommendation for a lay audience

Criterion 4: Availability of international polices to enable environments to comply with the recommendation

- Recommendations for the public
- Corresponding Recommendations for policy-makers







World Cancer Research Fund International

CUP GLOBAL Cancer Update Programme

Critical evaluation of bias has to start at the level of the individual study

Syntheses of studies in health risk assessment are key to derive conclusive results and several methods exist to assess study quality

But study quality can be challenging to assess; study quality assessment has to be included in the reporting of invidual studies

Studies should collect data that allow critical assessment of their findings (e.g. NRQ, secondary data for comparison, multiple ways of assessing exposures, ...)

But reality: lack of time, lack of funding, ...

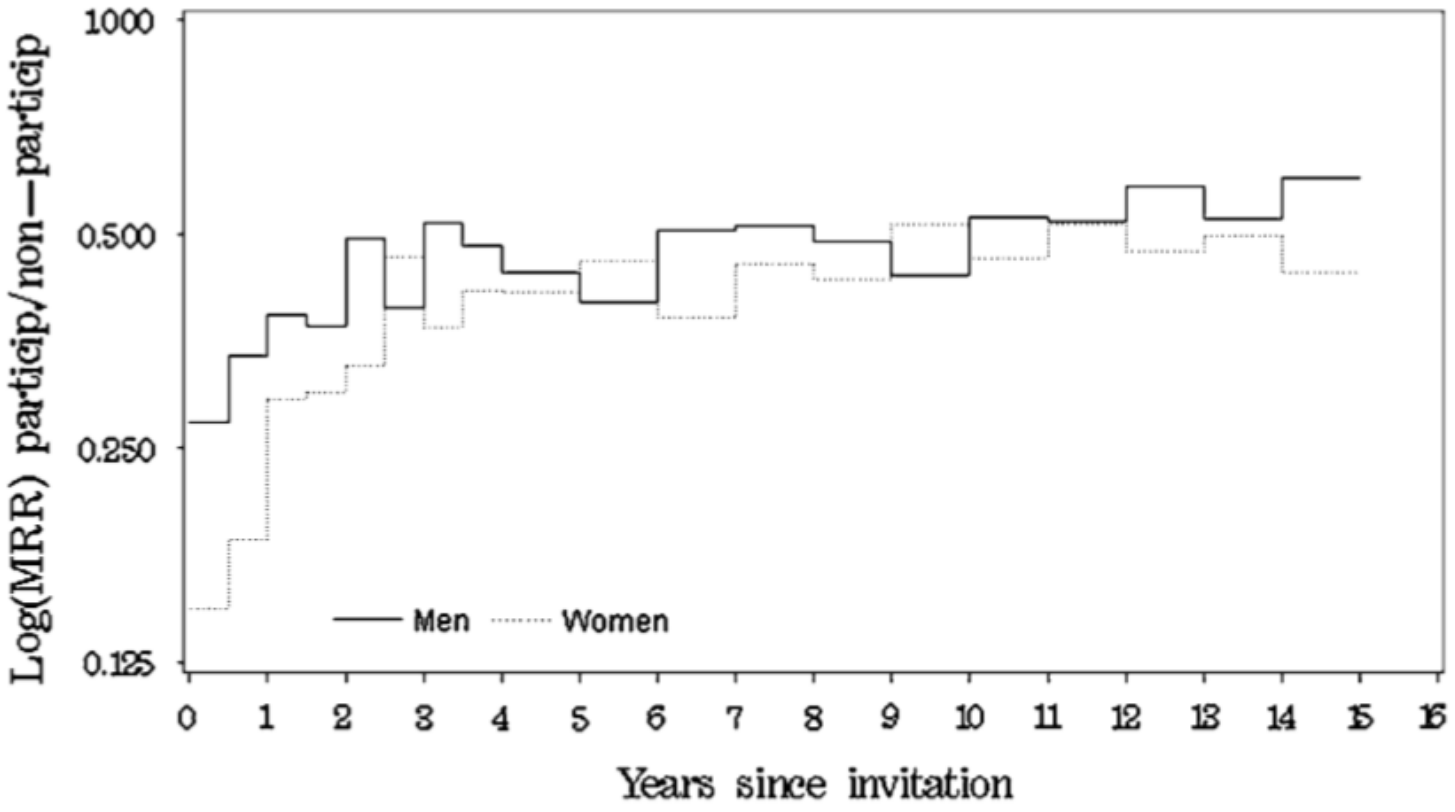


Fig. 2 Log rate ratio of overall mortality (*logMRR*) between participants and non-participants in the prospective Danish "Diet, Cancer and Health" Study stratified by sex

Eur J Epidemiol (2012) 27:837–845
DOI 10.1007/s10654-012-9739-x

METHODS

Mortality among participants and non-participants in a prospective cohort study

Signe Benzon Larsen · Susanne Oksbjerg Dalton · Joachim Schüz · Jane Christensen · Kim Overvad · Anne Tjønneland · Christoffer Johansen · Anja Olsen

Received: 8 May 2012 / Accepted: 5 October 2012 / Published online: 16 October 2012

Mortality in first 2 years after recruitment 4-6 times higher in non-participants

Stable ~2 times higher for 15 years

~4 times for alcohol-related deaths

Example: Bias evaluation in epidemiological studies on the use of mobile phones and the risk of glioma

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 208

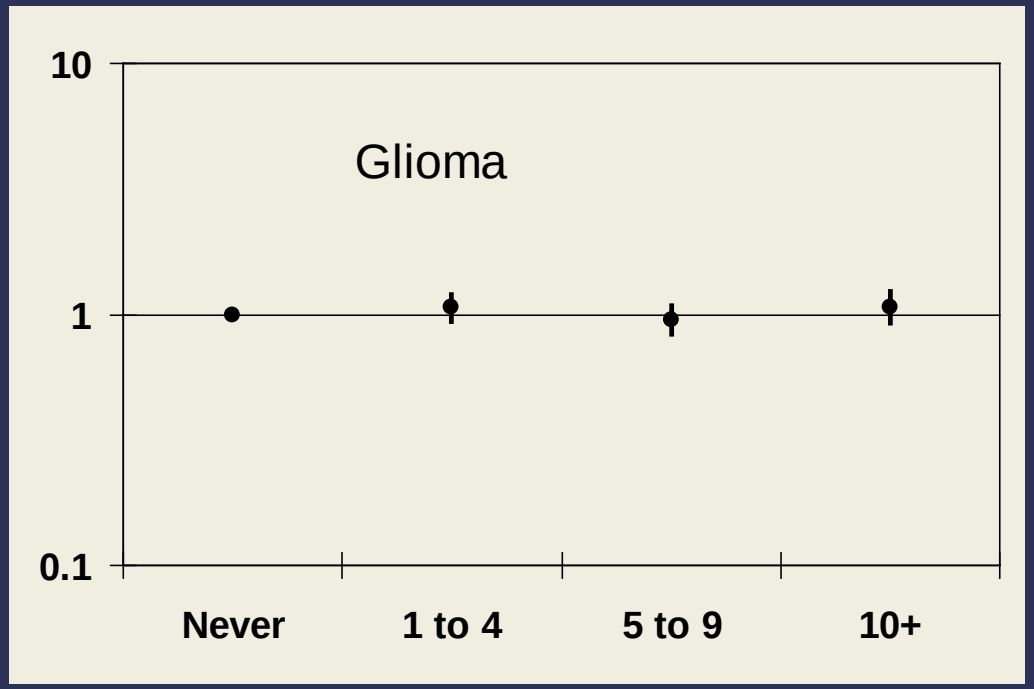
31 May 2011

IARC CLASSIFIES RADIOFREQUENCY ELECTROMAGNETIC FIELDS AS POSSIBLY CARCINOGENIC TO HUMANS

Lyon, France, May 31, 2011 -- The WHO/International Agency for Research on Cancer (IARC) has classified radiofrequency electromagnetic fields as **possibly carcinogenic to humans (Group 2B)**, based on an increased risk for **glioma**, a malignant type of brain cancer[1], associated with wireless phone use.

Cohort Studies (Denmark, UK (Women))

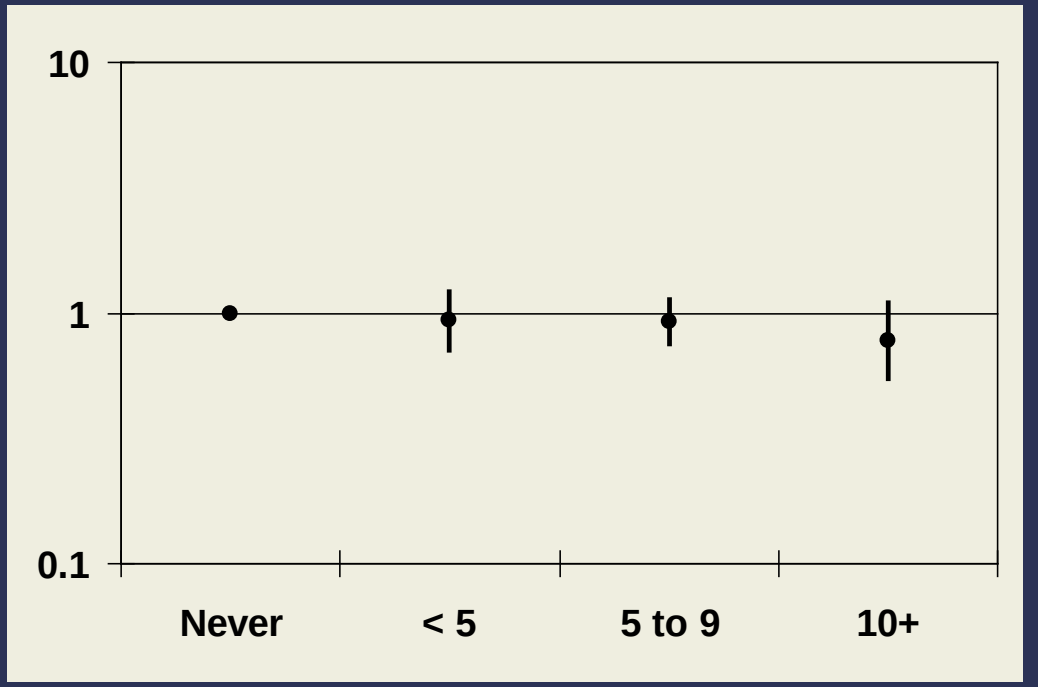
Individual risk from comparing the earliest subscribers for a mobile phone in Denmark (before 1995) with the rest of the Danish adult population



Years of subscription

Frei et al., BMJ, 2011

Individual risk from comparing never mobile phone users with mobile phone users by number of years of use within UK Million Women Study



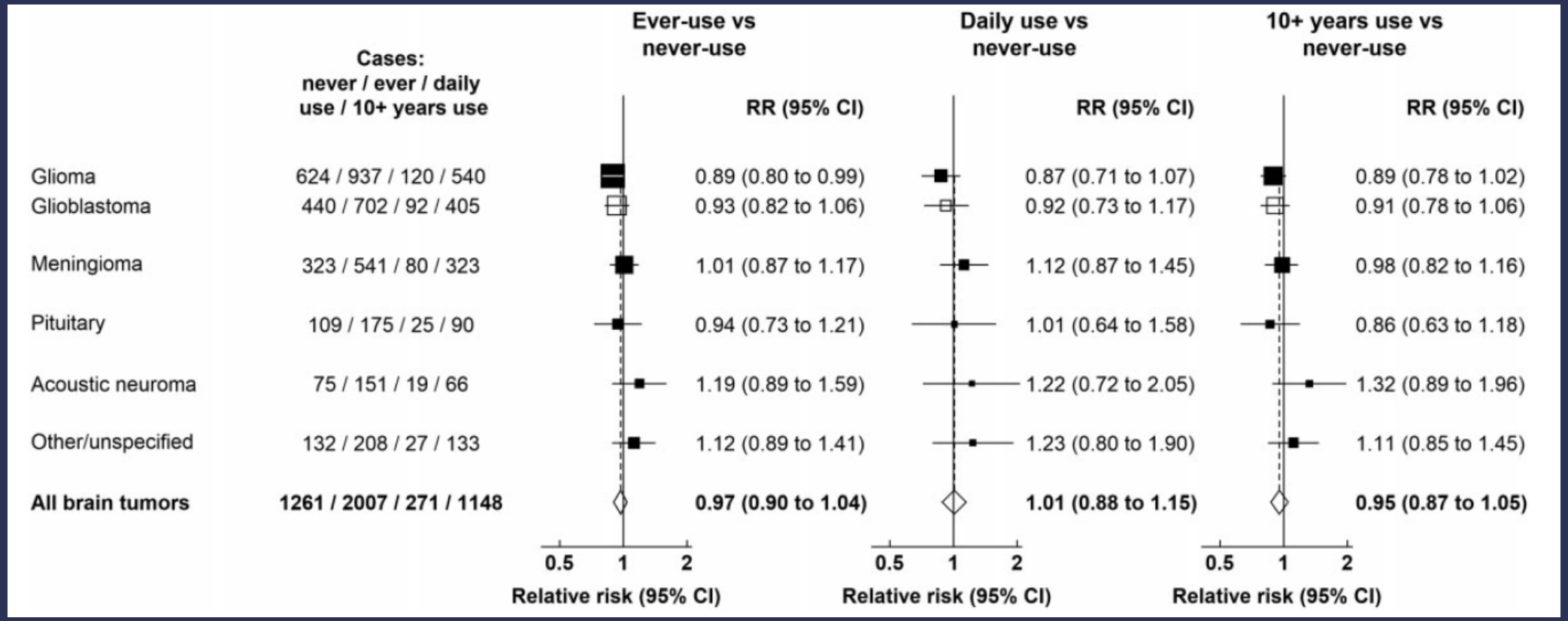
Years of mobile phone use

Benson et al., Int J Epidemiol, 2013

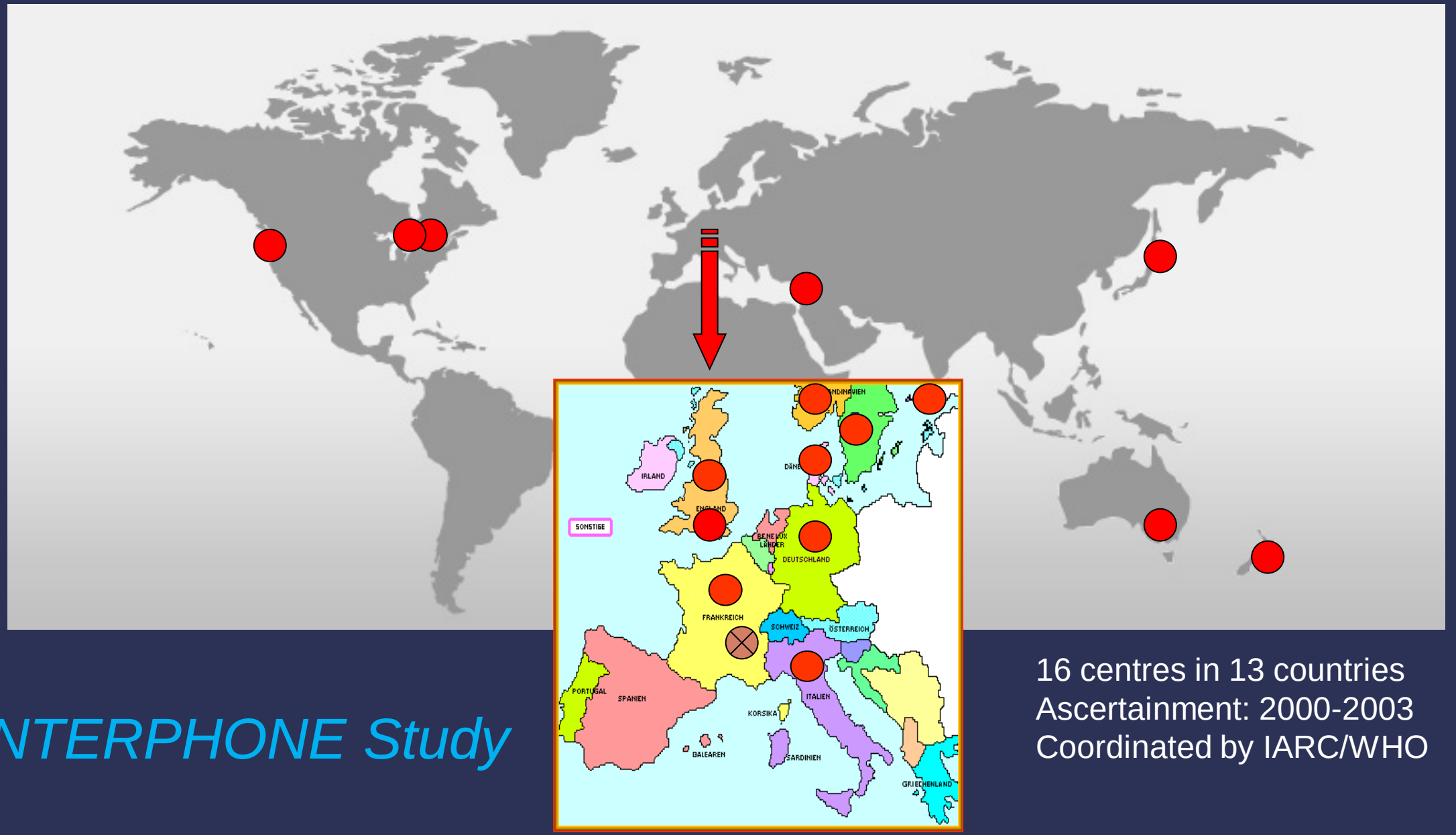
Update: UK Million Women Study

Update of individual risk from comparing never mobile phone users with mobile phone users by number of years of use within UK Million Women Study

No association with ever use, daily use, 10+ years of use or specifically with tumours in the most exposed area of the brain (temporal and parietal)



Schüz et al., J Natl Cancer Inst, 2022

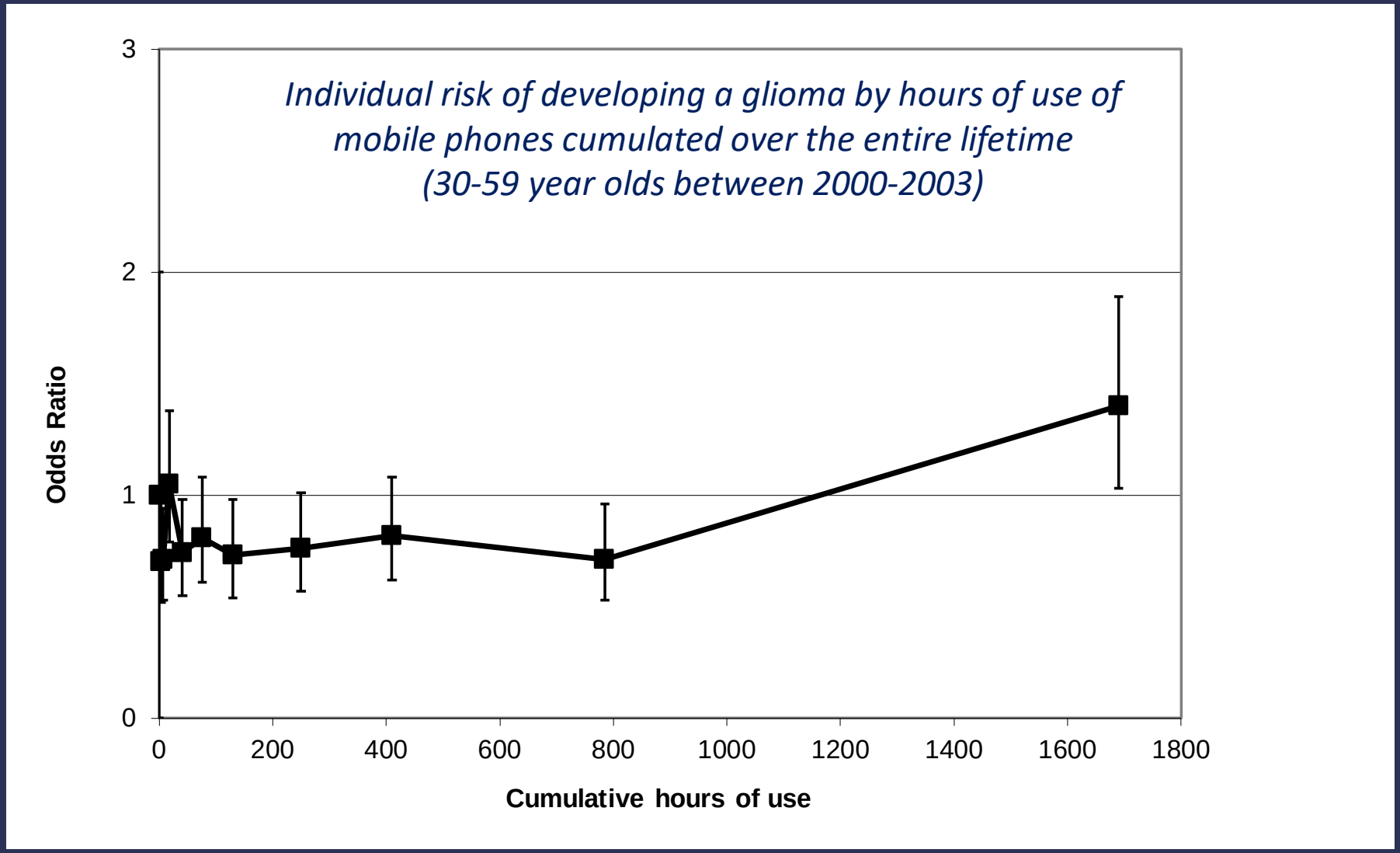


INTERPHONE Study

16 centres in 13 countries
Ascertainment: 2000-2003
Coordinated by IARC/WHO

Interphone Study Group, Int J Epidemiol, 2010

Interphone Study Group, Cancer Epidemiol, 2011



Population risk: *- about half of the population were never regular users of a mobile phone (reference group)*
- almost half of the population had no increased (or even slightly decreased) risk
- about 5% of the heaviest lifetime mobile phone users had moderately increased risk

Interphone Study Group, Int J Epidemiol, 2010

Problem #1
Use of mobile phone ≠ RF exposure to the head

2 W

~ 666 times

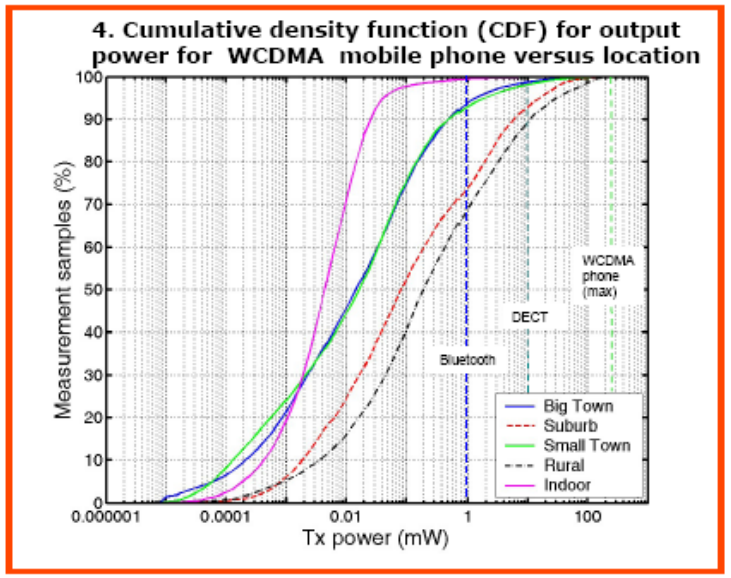
0.003 W

Lönn et al., Occup Environ Med, 2004

Vrijheid et al., Occup Environ Med 2009

SMP validation studies (INTERPHONE):
(based on >60000 individual calls)

- Cumulative use correlates sufficiently well with cumulative output power
- Due to poor network optimization (still in the early 2000s):
  - ~40% of calls at maximum power
  - average output power ~50% of max (2 W /8 /2 = 125 mW)



Problem #2
Random inaccurate recall of mobile phone use

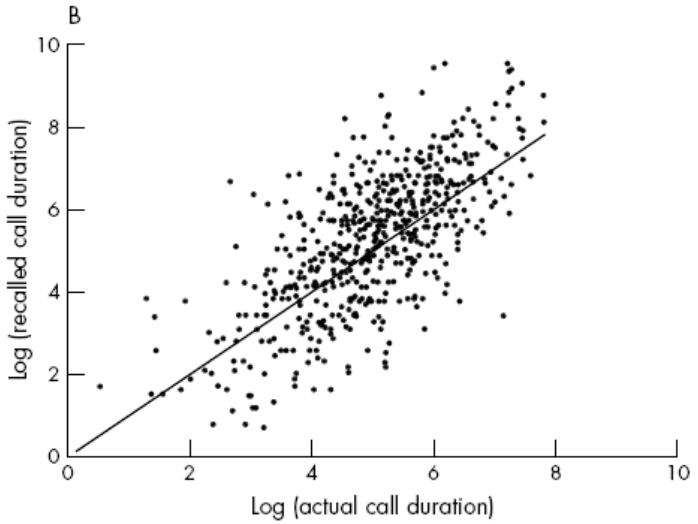


Figure 1 Scatter plot of (A) number of calls and (B) duration of calls (in minutes) reported in the questionnaire against the actual use recorded by operator or SMP (including line of equality).

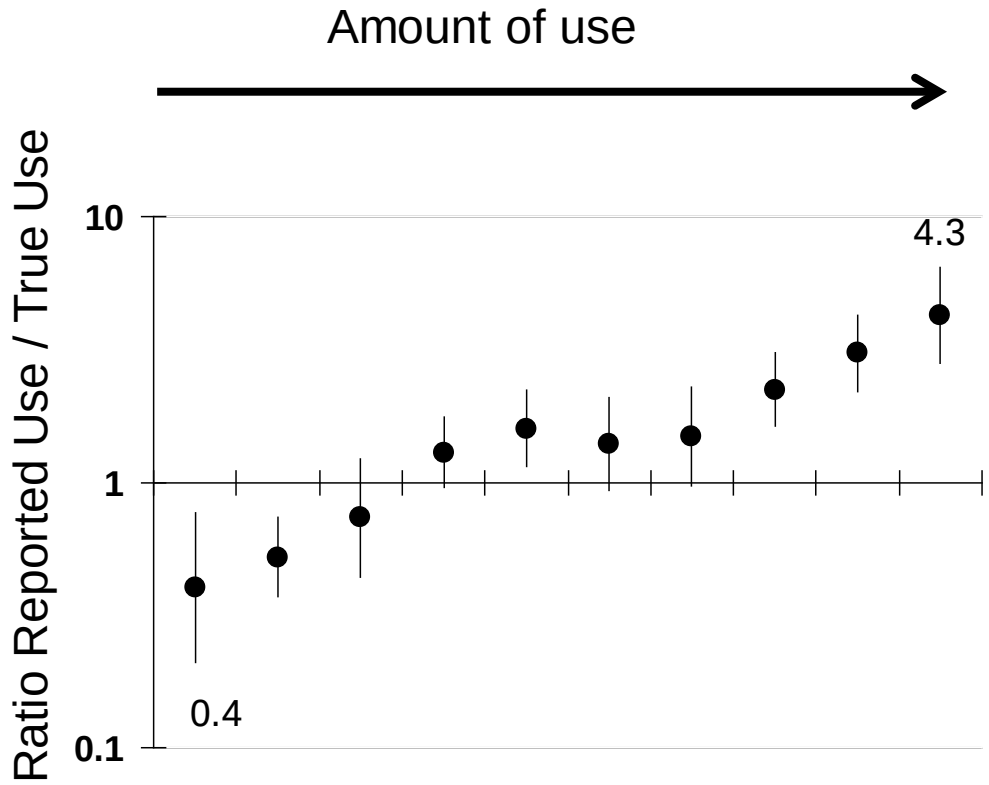
Underestimation of number of calls (20%)

Overestimation of duration of calls (42%)

< 50% of subjects between 50% and 200% of their actual use

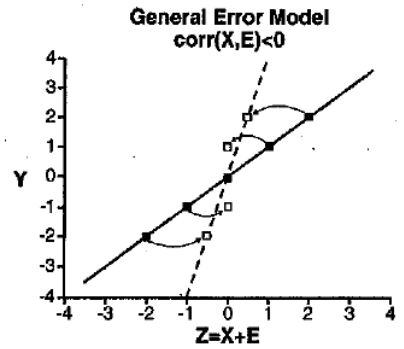
Vrijheid et al., *Occup Environ Med*, 2006

Problem #3
Systematic inaccurate recall of mobile phone use



Underestimation in light and overestimation in heavy users

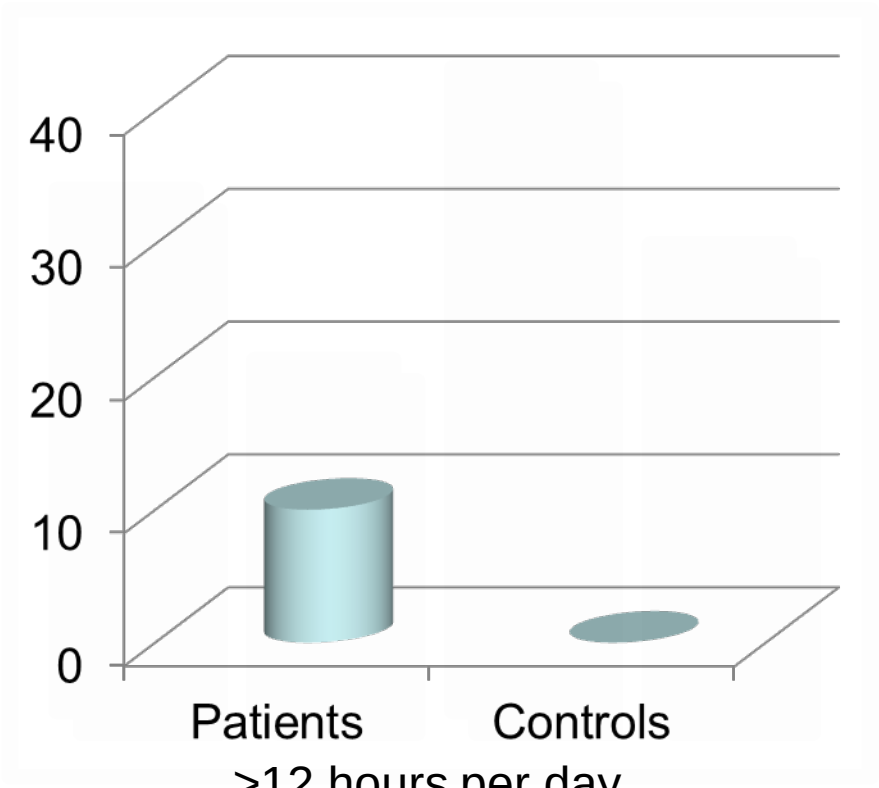
Tendency of more over-reporting in cases



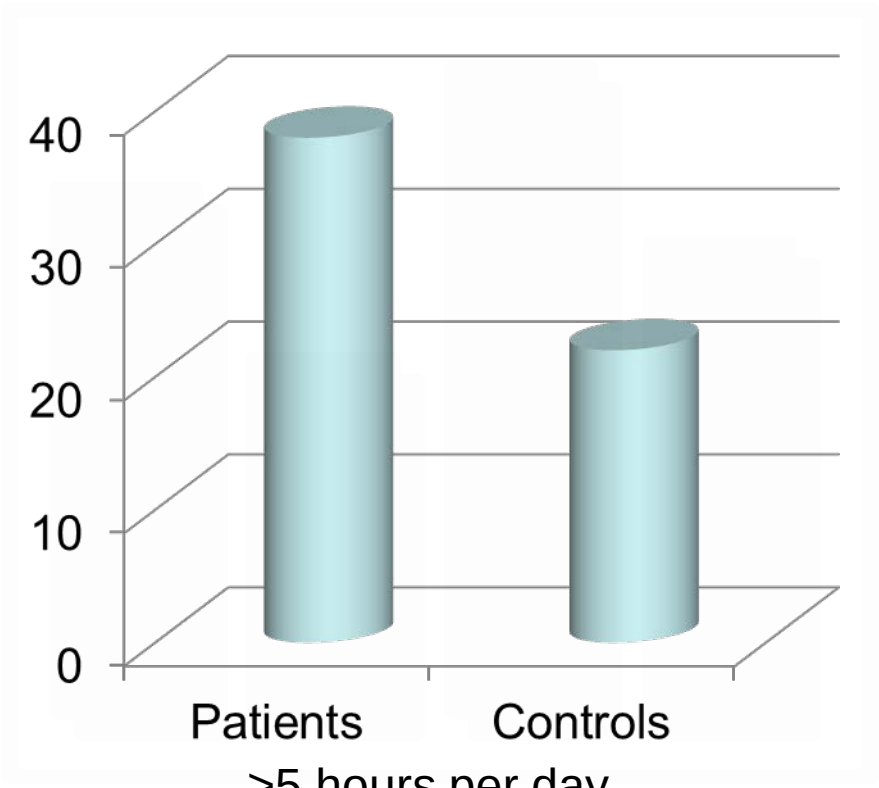
Vrijheid et al., J Expo Anal Env Epidemiol 2008

Wacholder, Epidemiol, 1995

Problem #4
Reporting patterns different in patients than in controls



>12 hours per day

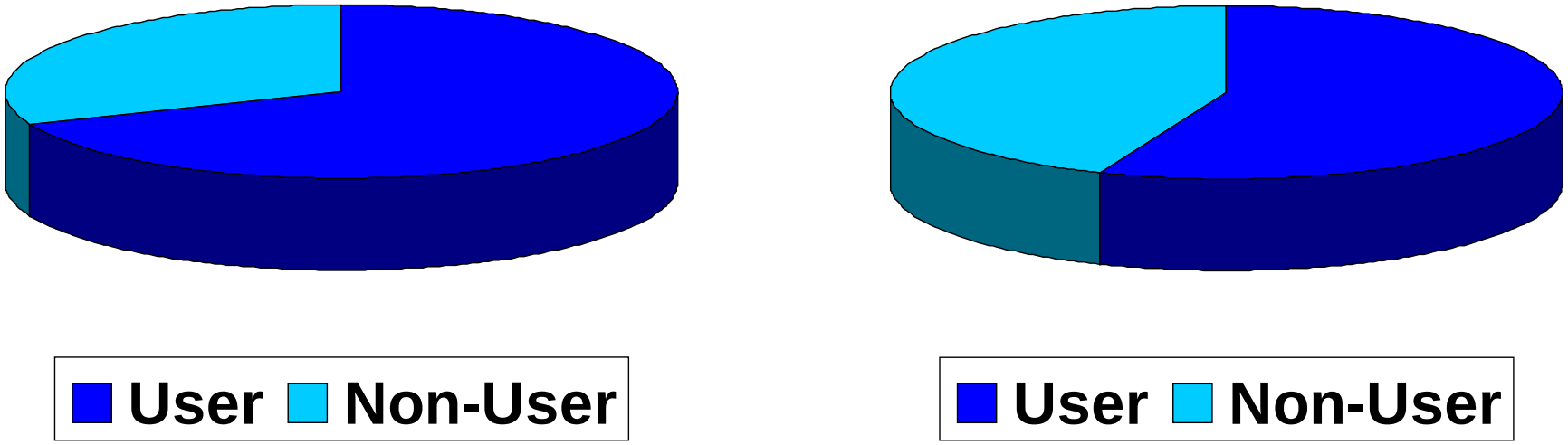


>5 hours per day

Interphone Study Group, Int J Epidemiol, 2010

Problem #5
Participation related to exposure of interest

Regular mobile phone users among
control participants and nonparticipants:



Vrijheid et al., Ann Epidemiol (2009)

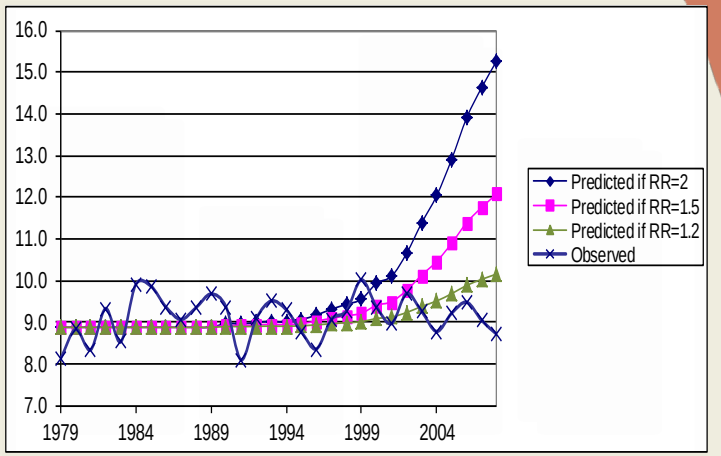
Summary of problems

	Self-reported use	*Effect*
Limitations		
- Use ≠ RF Exposure	⇔	Attenuation of possible association
- Random reporting error	⇔	Attenuation of possible association
- Systematic reporting error	⇗	Inflation of possible association
- Over-reporting	⇧	Spurious positive association
- Participation bias	⇩	Spurious inverse association

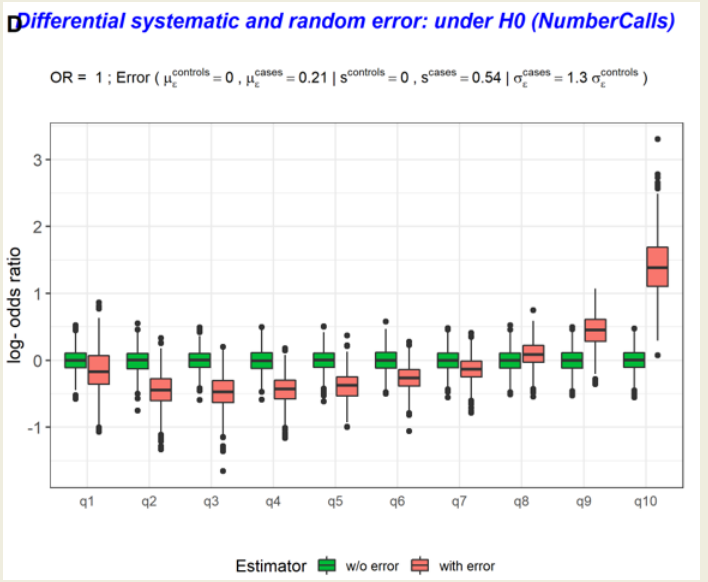
⇔ Towards null ⇗ Inflation ⇧ Spurious positive effect ⇩ Spurious protective effect

Results from the research program on radiofrequency electromagnetic fields and brain tumours

GliMoRi: Observed incidence rates of glioma in men in the Nordic countries are not compatible with mobile phone use-related increased glioma risks observed in some case-control studies, suggesting the latter are affected by bias (Deltour et al., Environ Int, 2022)



INTER-Cal: Modelling reporting errors from studies evaluating self-reported mobile phone use add evidence that the finding of an association between heavy mobile phone use and glioma risk of the Interphone study is caused by those reporting errors (Bouaoun et al., under review); main driver is larger variance in reporting error (measurement error) in cases compared to controls (differential error)



Emerging Challenges

Scientific: Even more precision in exposure assessment required

- to compare very low exposed to even lower exposed
- to study interactions, effect modifications, gene-environment
- to identify small individual risks

Conduct of studies: To overcome

- decreasing motivation to participate in studies (especially HIC)
- barriers in data and material sharing due to GDPR

External factors:

- increasing administrative workload for scientists
- overly cautious demands on observational studies from ethics
- too few funding frameworks include proper piloting or critical appraisal of findings

Conclusions

- Epidemiological studies will always have a prominent role in health risk assessment: *studying humans in real life*
- Critical appraisal of bias, error and confounding is key to distinct between causal associations, coincidental associations and spurious associations
- Assessment of study quality has to start at the level of the individual study
- Some emerging challenges make the conduct of epidemiological studies in Europe more difficult than it was before

Acknowledgments

IARC's
Environment and Lifestyle Epidemiology Branch

IARC Monographs Program

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Head of Evidence Synthesis & Classification Branch,
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