# Cell phones and cancer risk

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**DCEG Radiation Epidemiology and Dosimetry Course 2019**

# Declaration of interests

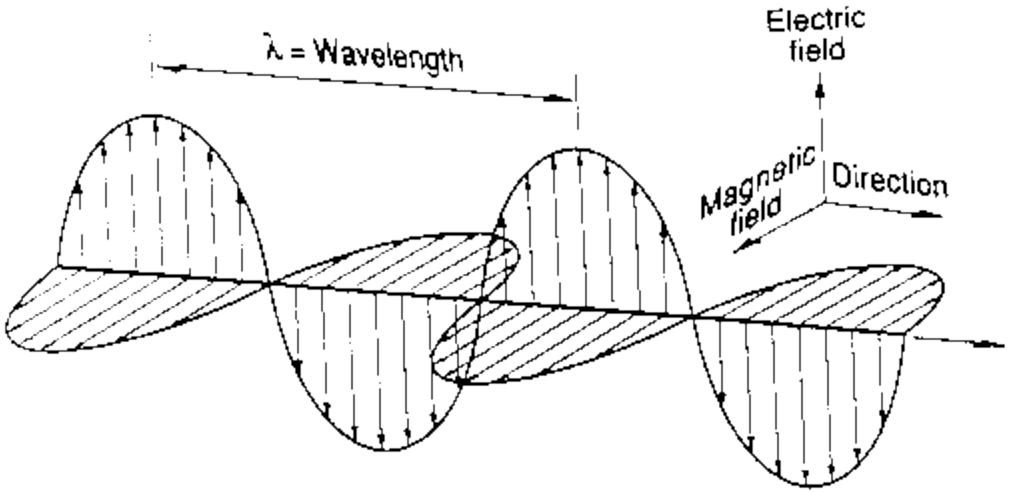
- Member of INTERPHONE study group, PI of the Finnish Interphone study
- Member of COSMOS study group, PI of the Finnish COSMOS study
- Former member of the SCENIHR committee, ICNIRP PG, and SSM Expert Group
- Research funding through governmental research program and/or firewall from Nokia, network operator Telia and Mobile Manufacturers' Forum (currently MWFAI)

# Outline

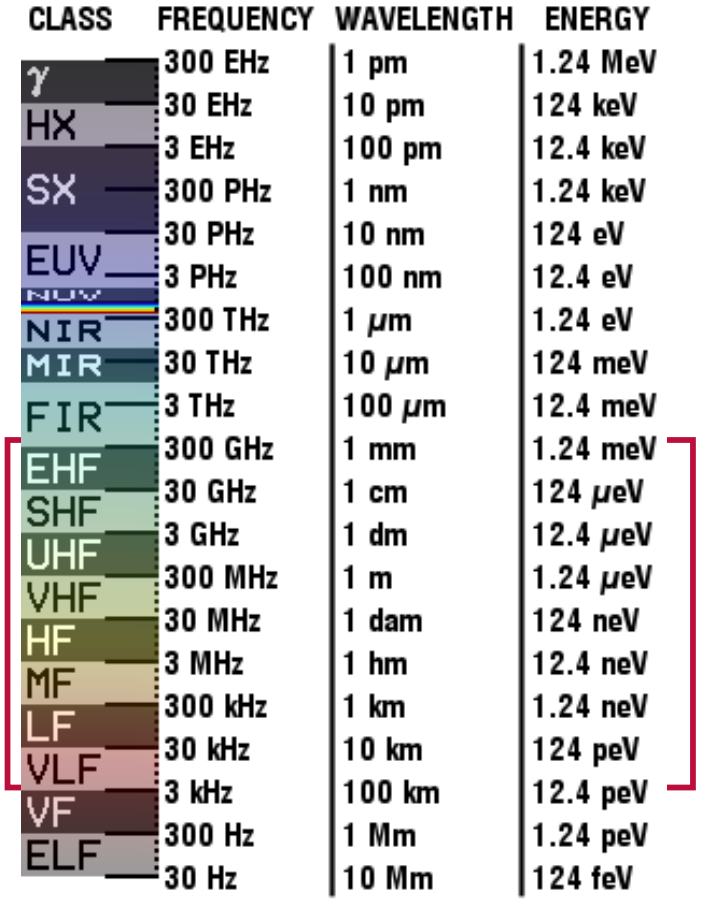
- Background: Introduction to RF-EMF and cellular phones
- Issues in epidemiological studies of cellular phones
- Results of major epidemiological studies
- Analysis by location
- Incidence trends
- Overall assessment

# Background

# Electromagnetic field

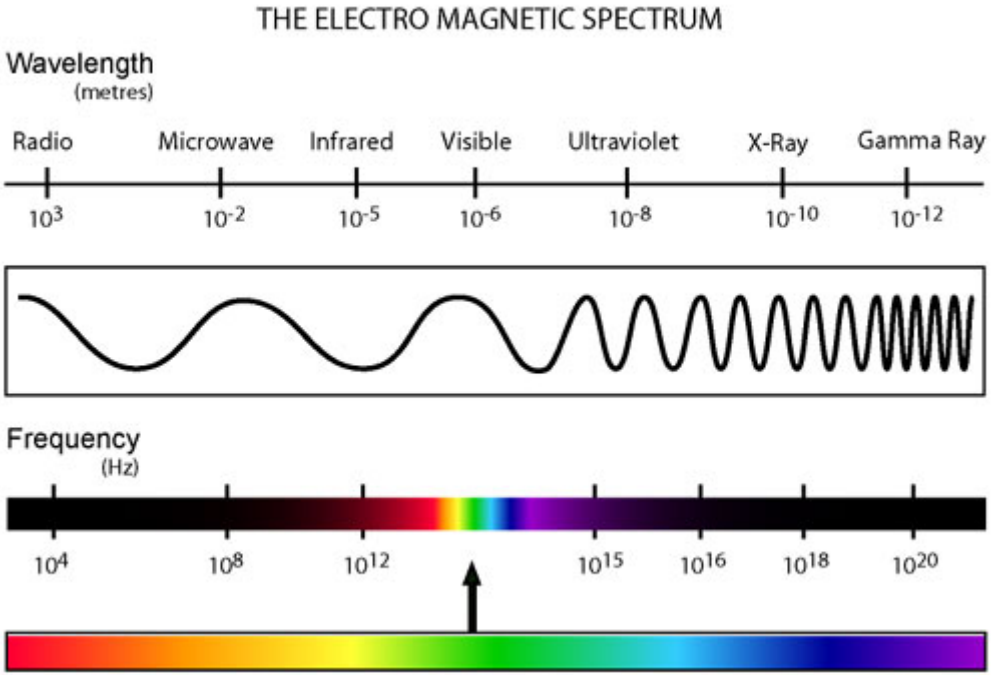


# Radiofrequency fields



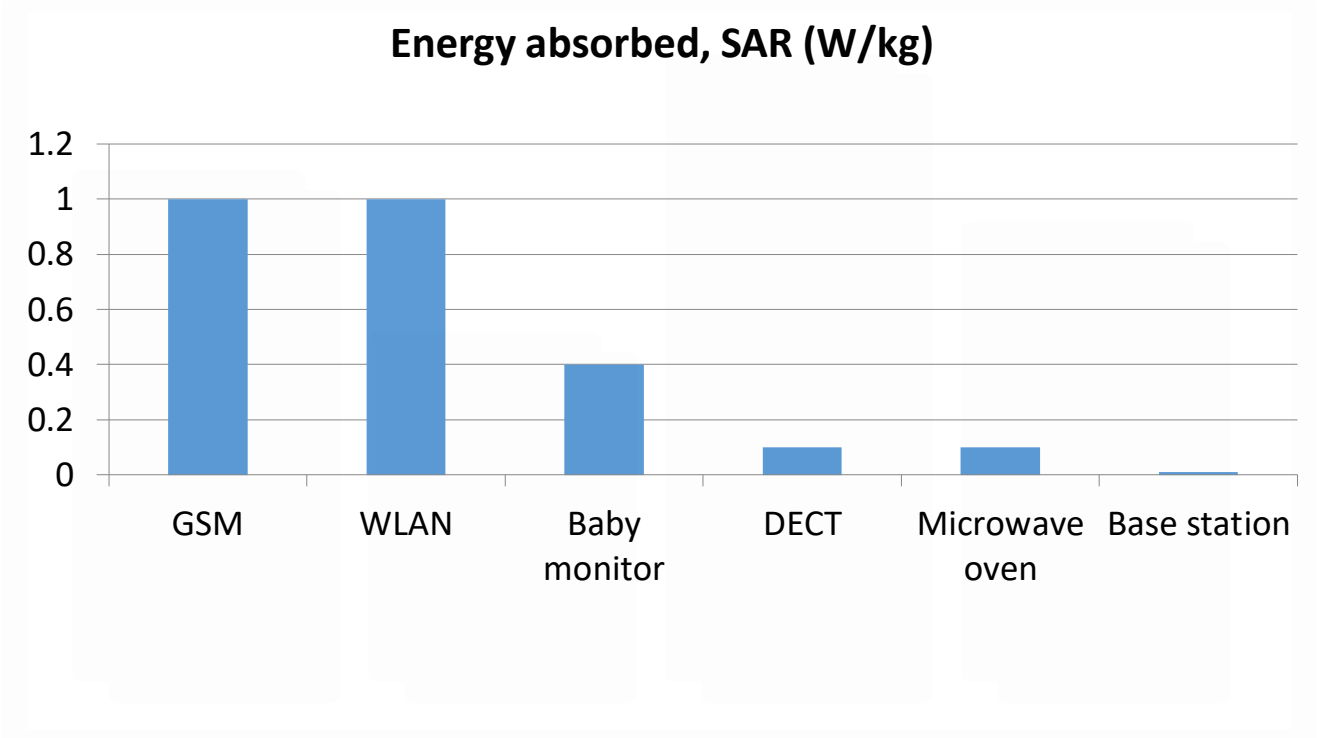

From 3 kHz to 300 GHz

# The Electromagnetic Spectrum

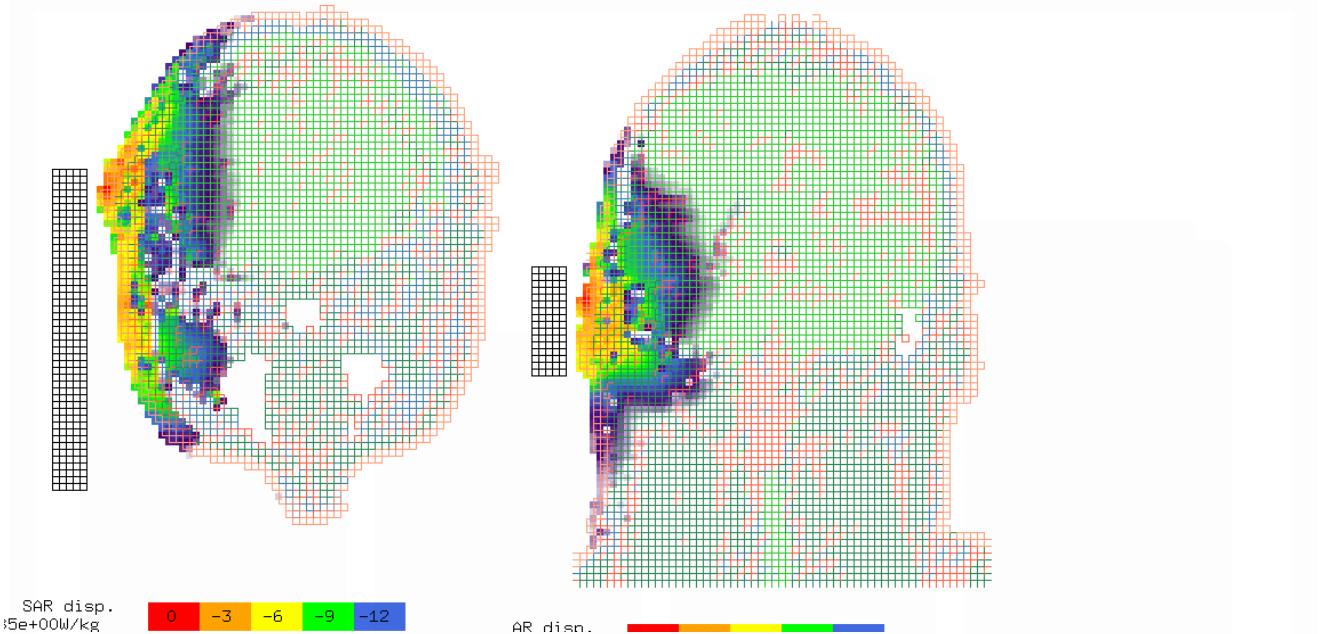


# Sources of radiofrequency fields

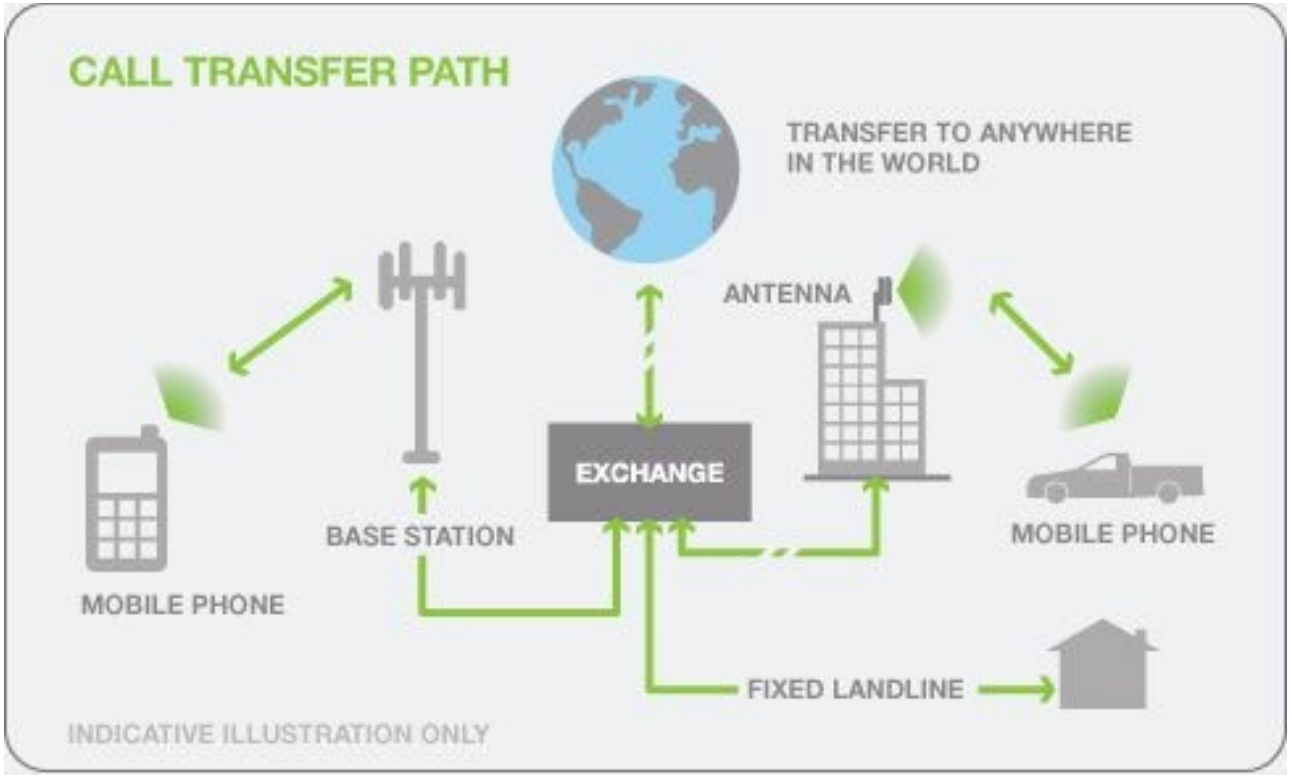
# RF field from various sources



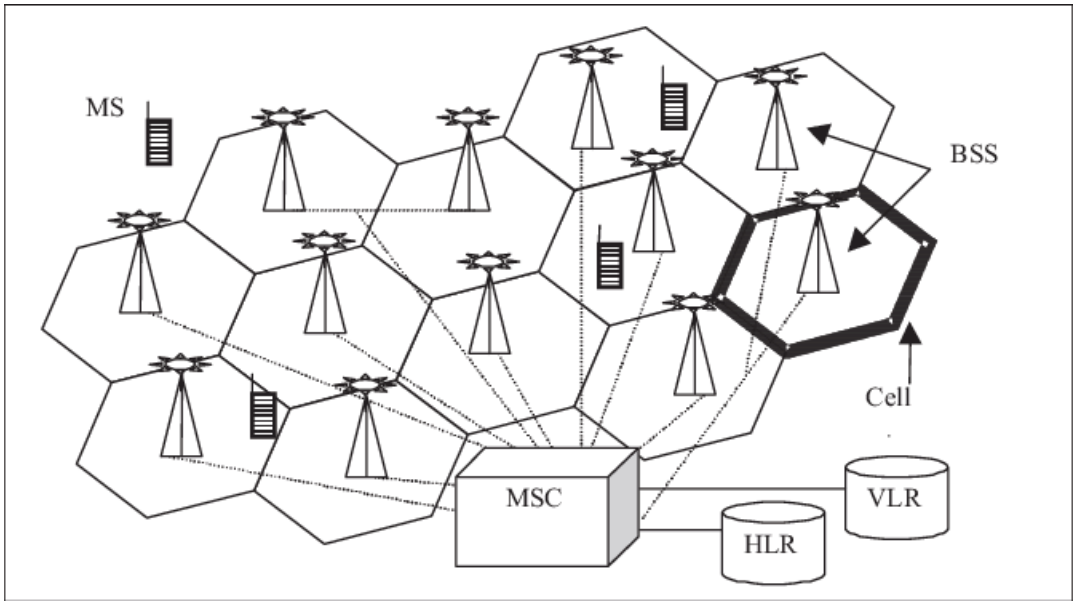
# Field strength (SAR) from a mobile phone



# How do cellular phones work?



# Why is it ‘cellular’?




- Area covered by a base station is a ‘cell’
- Base stations linked to each other to form a network

# Issues in epidemiological studies of cellular phones

# Introduction

- Health risks from exposure to radiofrequency electromagnetic fields a topic of ’epidemiology wars’
- Highly contested interpretation of the evidence
- Some researchers unfailingly report major increases in risks that are not replicated in other studies
- Are mobile phones the ‘new tobacco‘? An emerging major threat to public health?
- Comprehensive review of expert panels by IARC, AGNIR, SCENIHR, SSM and others

# Major challenges

- Exposure assessment
- Recall bias in case-control studies
- Possible interference of brain tumor on recall and cognitive function
- Lack of identified biological mechanism, and hence a proper concept of dose (or even identification of the main aspect relevant for risk)
- Unclear latency

# Exposure assessment for mobile phone use

- Questionnaire or interview
  - Retrospective
  - Inaccurate, possibility of bias
- Network operator records
  - Usually only ownership of a subscription
  - Who is the actual user?
  - Corporate subscriptions?
  - Amount and mode of use?
- Output power best proxy indicator of SAR
  - Not available in any epidemiological study

# Determinants of cell phone output power

- Network/phone technology
  - Increasing efficacy, lower output with each generation NMT>>GSM>>UMTS>>LTE
  - Automatic power control: Minimal power needed for proper transmission
- Proximity to base station
  - If heavy traffic, a call can be referred to a more distant base station
- Calling while in transport
  - Wave-like increases and decreases in output power (first decreasing and then increasing distance)
- Rural area wth higher power
- Hands-free devices minimise the exposure to the head (do  not affect power)

Sources: Lönn 2004, Erdreich 2007, Vrijheid 2009, Cardis 2011, Kelsh 2011, Persson 2012

# How accurate is recalled usage data? (1)

- Number of calls underestimated and duration overestimated
- Agreement between reported and recorded diminished with time
- Kappa 0.66 - 0.51 - 0.31 for quintiles of call duration
  - Kiyohara JESEE 2018: Comparison of recorded (SMP phone) and reported, N=94
  - Reported after the 1-month study period, at 1 year and at 4 years
- Kappa for call duration 0.50, number of calls 0.39
- Overreporting x1.7 for call numbers, x2.8 for all duration
  - Parslow Radiat Prot Dosim 2003 questionnaire vs operator data for 6-mo period, N=93

# How accurate is recalled usage data? (2)

- Mireku et al. *Environ Res* 2018
- 350 participants with self-reported vs. operator-recorded call data
- Call duration overestimated by 45-59% of participants (underestimated by 11-16%)
- Weighted kappa 0.08-0.10 for call duration (7 categories)
- Sensitivity for identifying heavy use 13%

- Toledano *Int J Hyg Environ Health* 2018, 67,947 participants of COSMOS study
- Self-reported vs. operator-recorded call data
- Weighted kappa 0.50 for call duration (six categories)

# Issues in recall and reporting in cases: Recall bias

- A form of information bias
- Typical for case-control studies with self-reported exposure
  - Cases interviewed after dg about exposure prior to dg
- Classically, cases are highly motivated, want find an explanation for their disease, attribute it to a specific factor
- Therefore, provide a more complete and comprehensive account of their exposures than controls
  - Root cause is under-reporting of exposure in cases
- In addition, possible over-reporting (exaggeration) of exposures in cases
  - Not classical form of recall bias
  - A case knows side of brain tumor, which could affect reported laterality of use

# Issues in recall and reporting in cases (2)

- Cognitive and memory function may be affected by the tumor
- Physiological effect depending on the anatomic site
- Psychological impact of severe major disease, a life-changing effect
- Lower quality of data in cases??
- Mainly for maligant tumors, less of an issue for meningioma, schwannoma/neuroma

# Is there recall bias in reporting?

Overreporting of use in distant past more pronounced in cases than controls

- Vrijheid et al. *J Expo Sci Environ Epid* 2009

Mean difference in year of start between reported and recorded

- Cases +0.25
- Controls -0.51
- 96 vestibular schwannoma cases and 111 controls
- Pettersson et al. 2015

# Epidemiological findings

# Evidence from epidemiology

- Glioma, meningioma, schwannoma/neurinoma
- Case-control studies: Interphone, Hardell, CEFALO, CERENAT
- Cohort studies: Danish subscribers, UK Million Women
  - Less prone to recall bias
- Case-case studies: Within Interphone (Larjavaara, Cardis, Grell)
- Time trend analyses: Nordic countries, UK, US, other populations

# Early studies of cellular phones and cancer

| Reference | Cases | Dg years | Duration of use |
|---|---|---|---|
| Muscat 2000 | 469 brain cancers | 1994-1998 | Max 4+ yrs (mean 2.8 yrs) |
| Inskip 2001 | 489 gliomas, 197 meningiomas, 96 neurinoma | 1994-1998 | Max 5+ years (22 cases) |
| Auvinen 2002 | 398 brain cancer, 34 salivary gland tumors | 1996 | Max >2 years (17 cases) |
| Lönn 2006 | Salivary gland | 2000-2002 | Max >10 yrs (6 cases) |
| Sadetzki | Salivary gland (parotid) | 2001-2003 | Max >10 years (13 cases) |

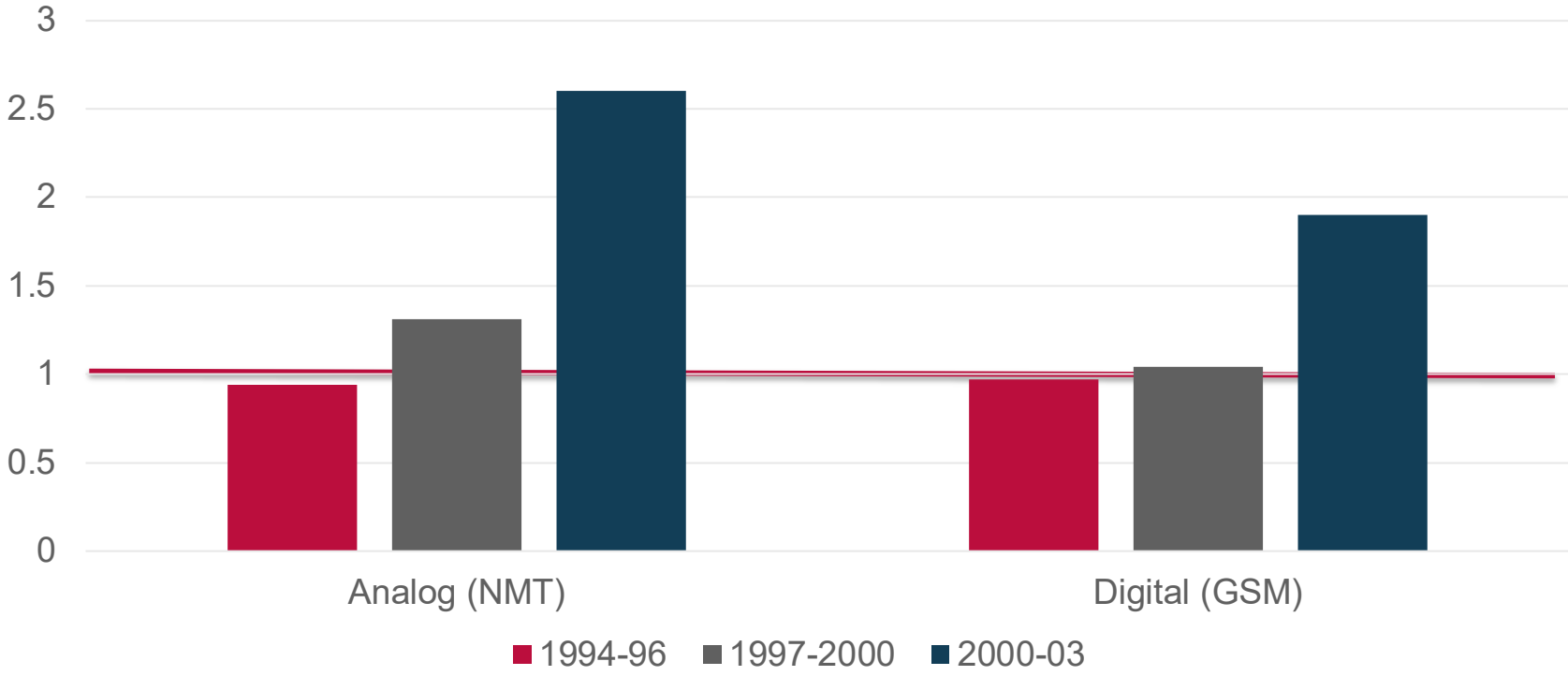
U.S. Cohort of 255,868 subscribers with 6 brain cancer deaths in 1-year follow-up (Dreyer et al. 1999)

# Major studies of cellular phones and cancer

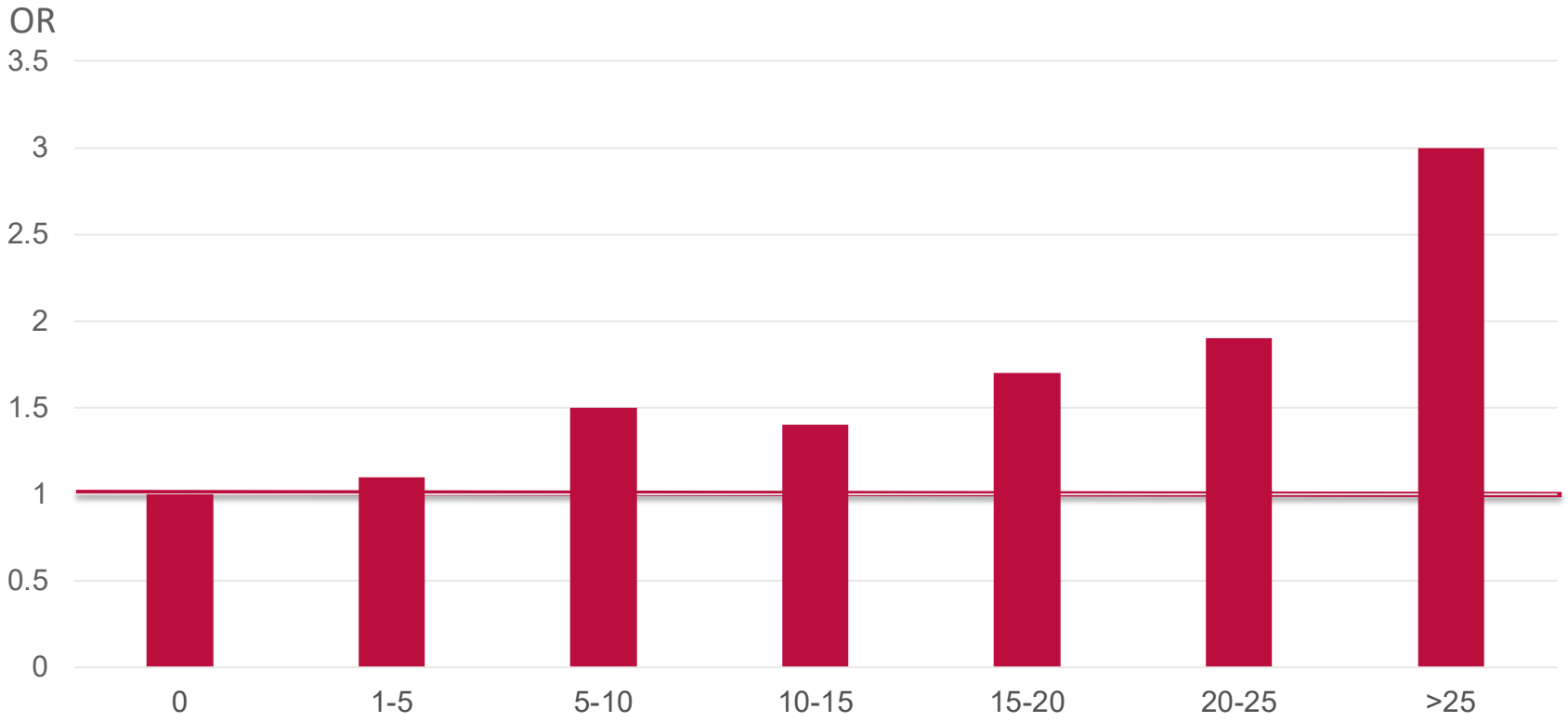
| Reference | Glioma | Meningioma | Acoustic neurinoma |
|---|---|---|---|
| Hardell | 382/1844 | 346/1625 | 58/316 |
| Interphone | 252/2708 | 110/2409 | 68/1105 |
| Yoon | -/285 | - | - |
| Coureau | 22/757 | 10/582 | - |
| Han | - | - | 92/343 |
| Pettersson | - | - | 103/422 |
| Frei | 117/356 | 29/80 | 15/404 |
| Benson | 135/571 | 63/251 | 14/96 |

Aydin et al. JNCI 2011: Childhood and adolescent brain tumors, no long term use

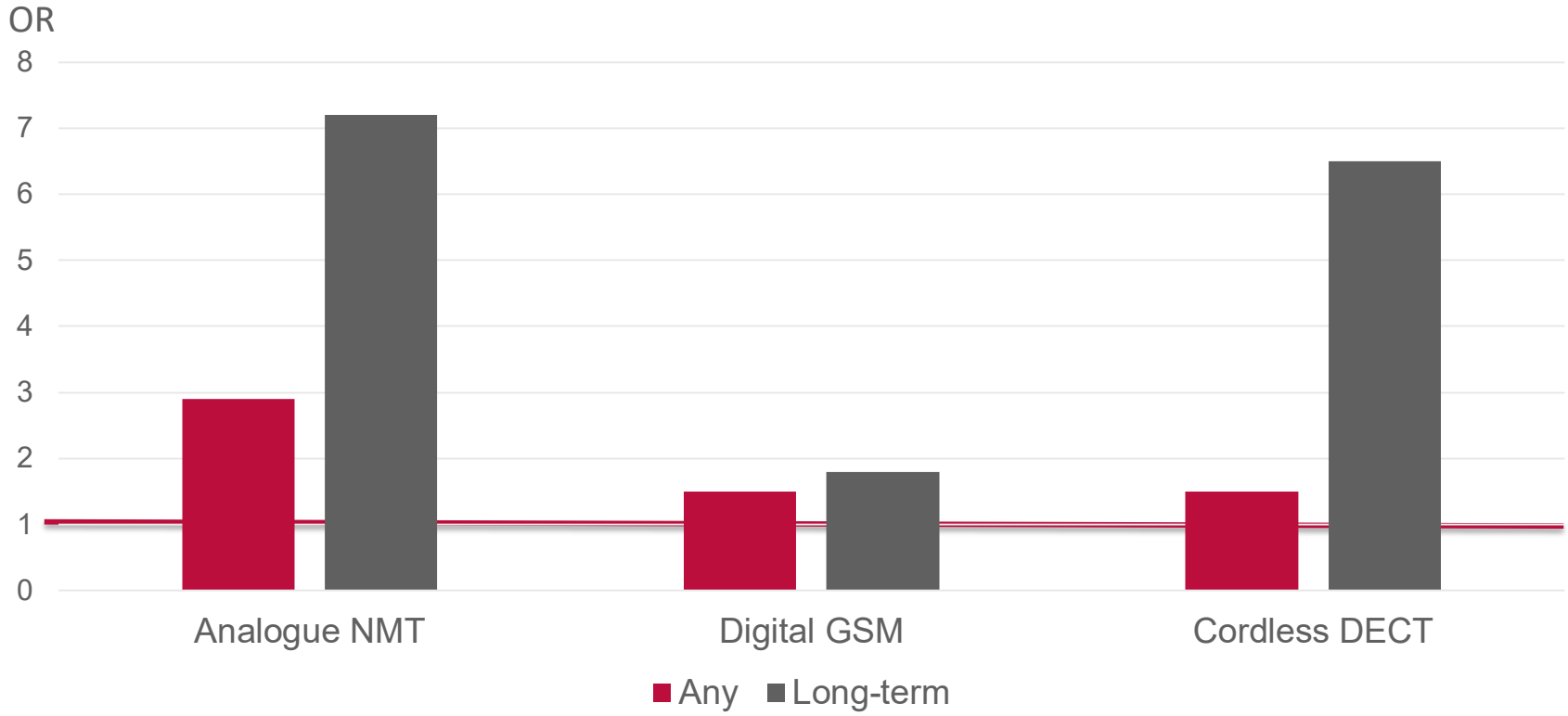
# Glioma risk with any mobile phone use in Hardell studies



# Glioma risk with duration of use in Hardell studies

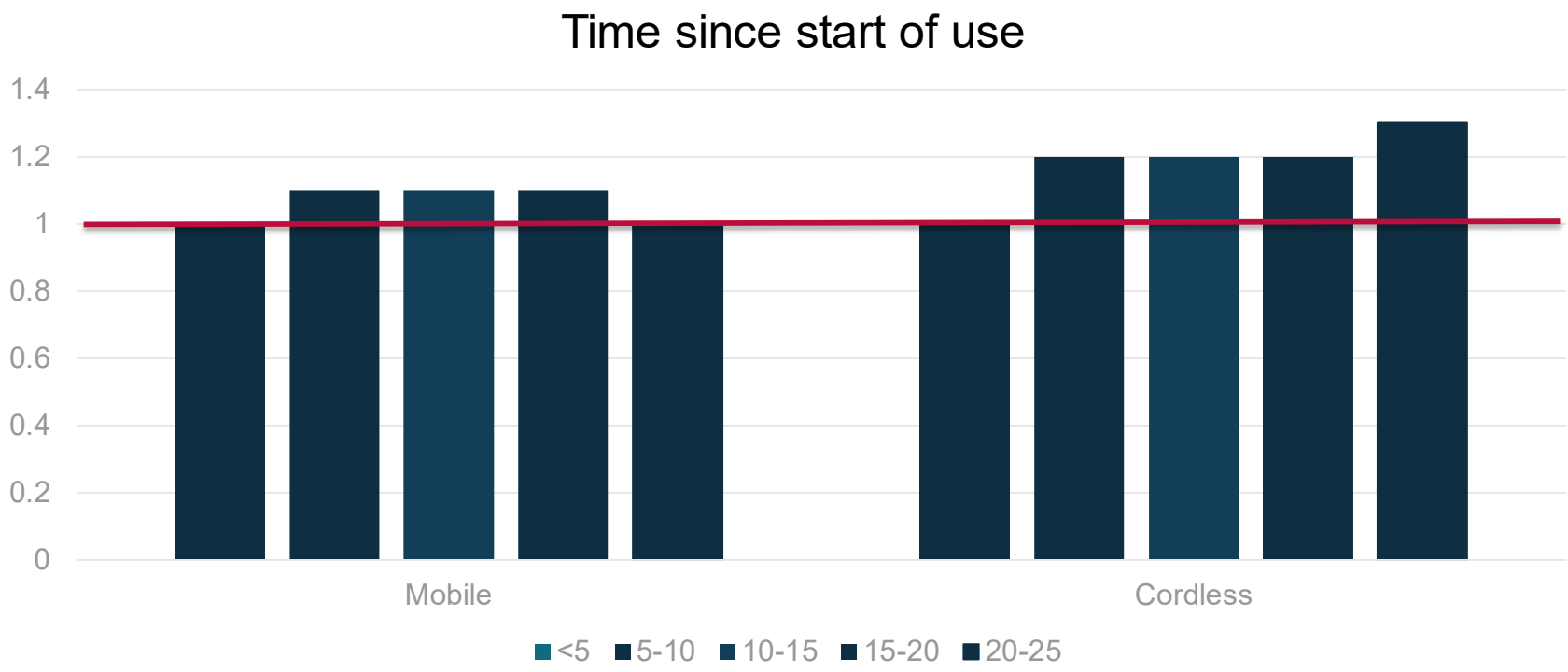


# Acoustic neuroma in Hardell studies




*Hardell et al. 2013*

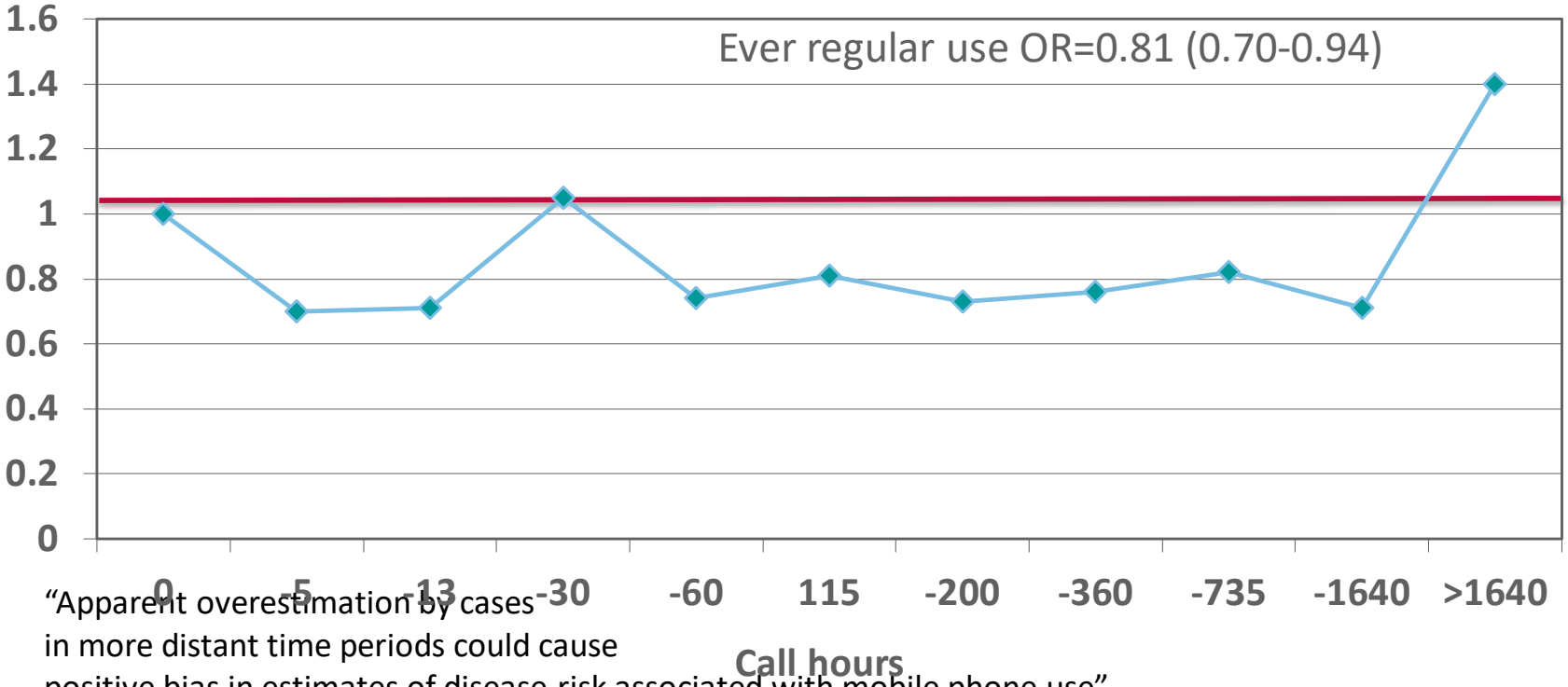
# Meningioma risk in Hardell studies



# Interphone study

- International collaborative study in 13 countries
- Glioma, meningioma, acoustic neuroma (vestibular schwannoma)
- Cases diagnosed 2000-2004
- Cases enrolled prospectively with interview an average 3 mo from dg
- Participation 65% cases and 53% controls
  - Proxy interviews for 13% of glioma cases

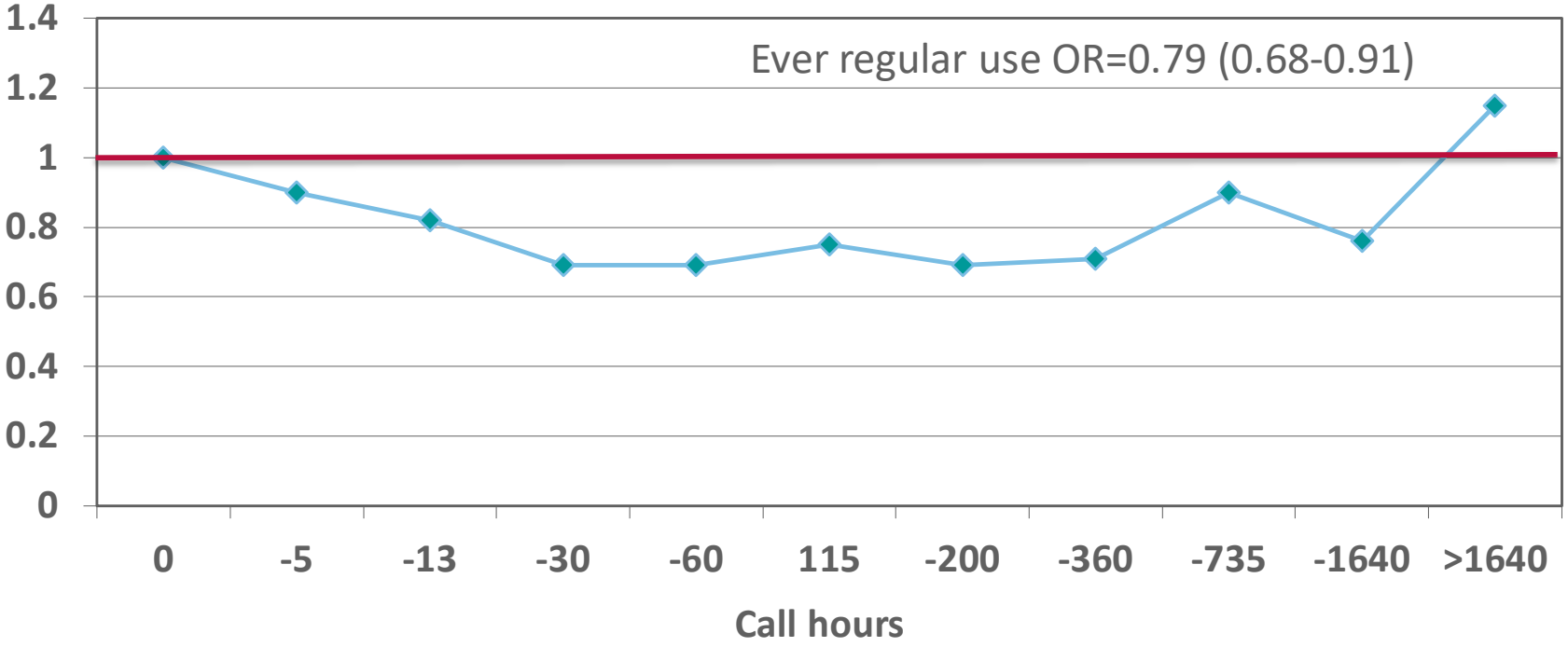
# Glioma and call-time in Interphone




"Apparent overestimation by cases in more distant time periods could cause positive bias in estimates of disease risk associated with mobile phone use"

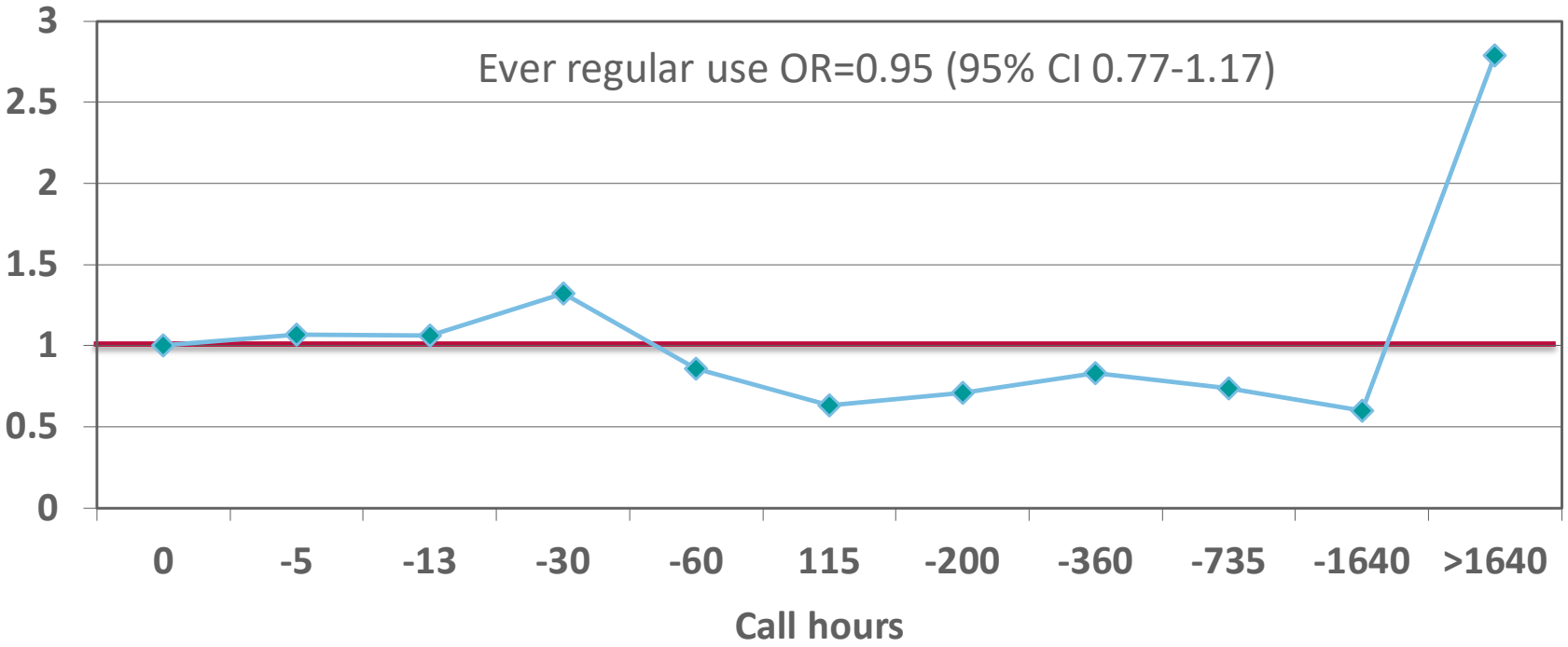
Interphone study group, *Int J Epid* 2010

# Cumulative call-time and meningioma risk




Interphone study group, *Int J Epid* 2010

# Cumulative call-time and acoustic neuroma

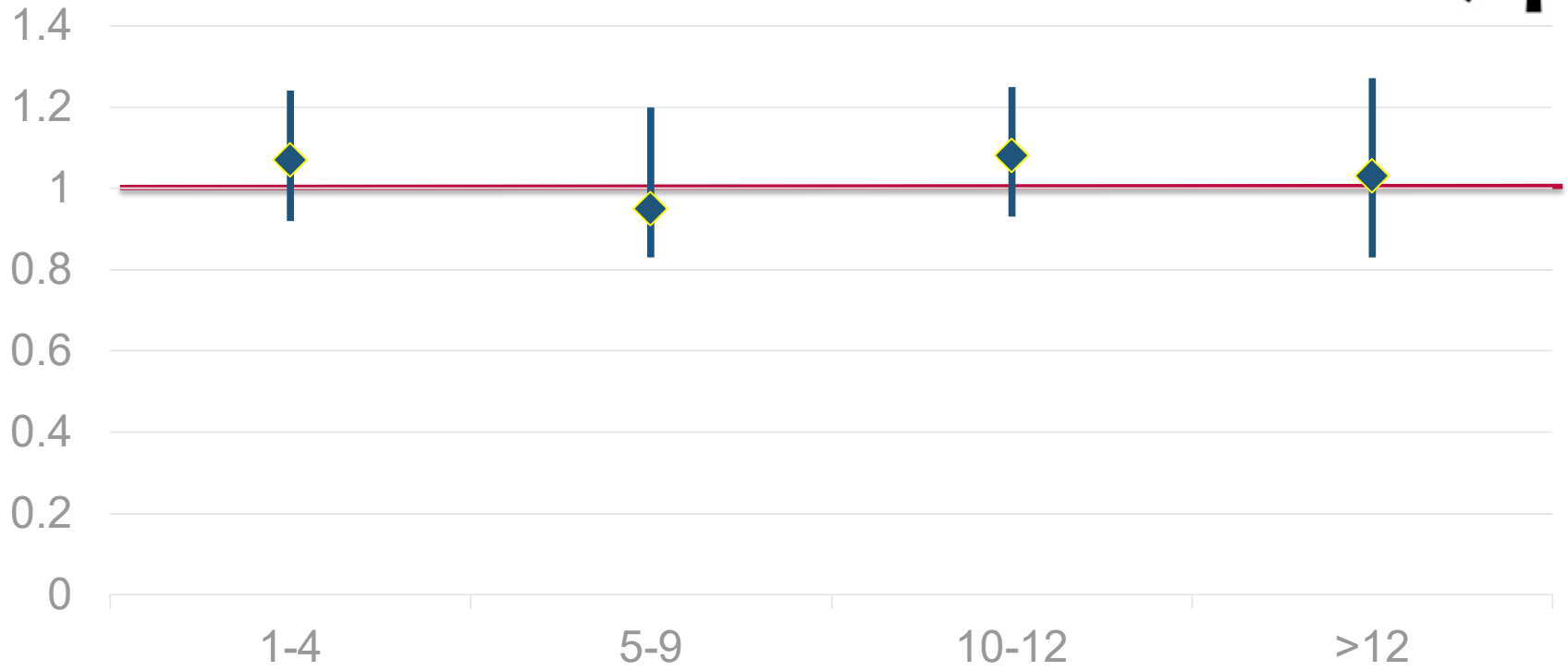



Schuz et al, *Cancer Epidemiol* 2011

# Danish cohort study

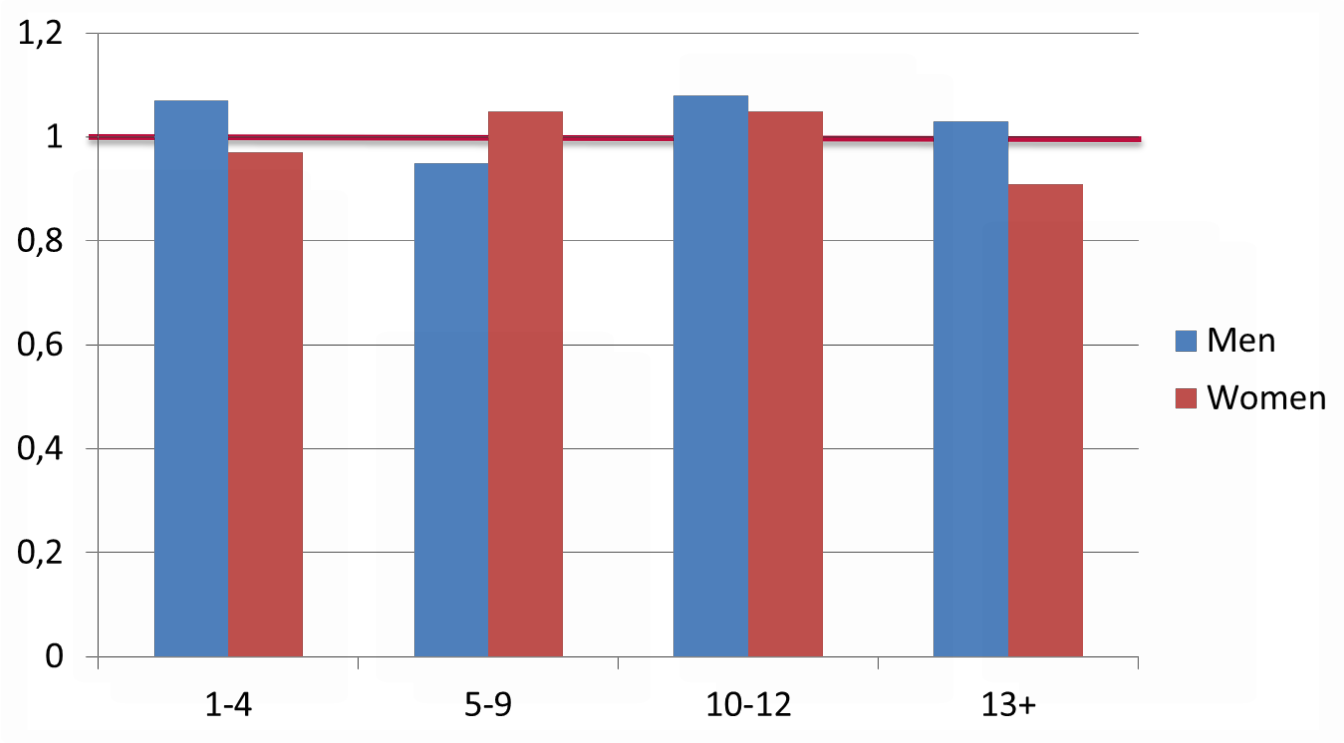
- Frei 2011, Schuz 2006, 2011, Poulsen 2012, 2013, Johansen 2001
- Exposed group: 358,403 subjects with private subscription in 1982-1995
  - Excluding 28% with corporate-owned subscription
- Poisson regression analysis
  - Confounders: Income, education
- Follow-up 1990-2007 (mean length 10.6 yrs)
  - 10,729 CNS tumors

# Duration of use and brain tumor incidence




Frei et al. 2011

# Duration of use and CNS cancers

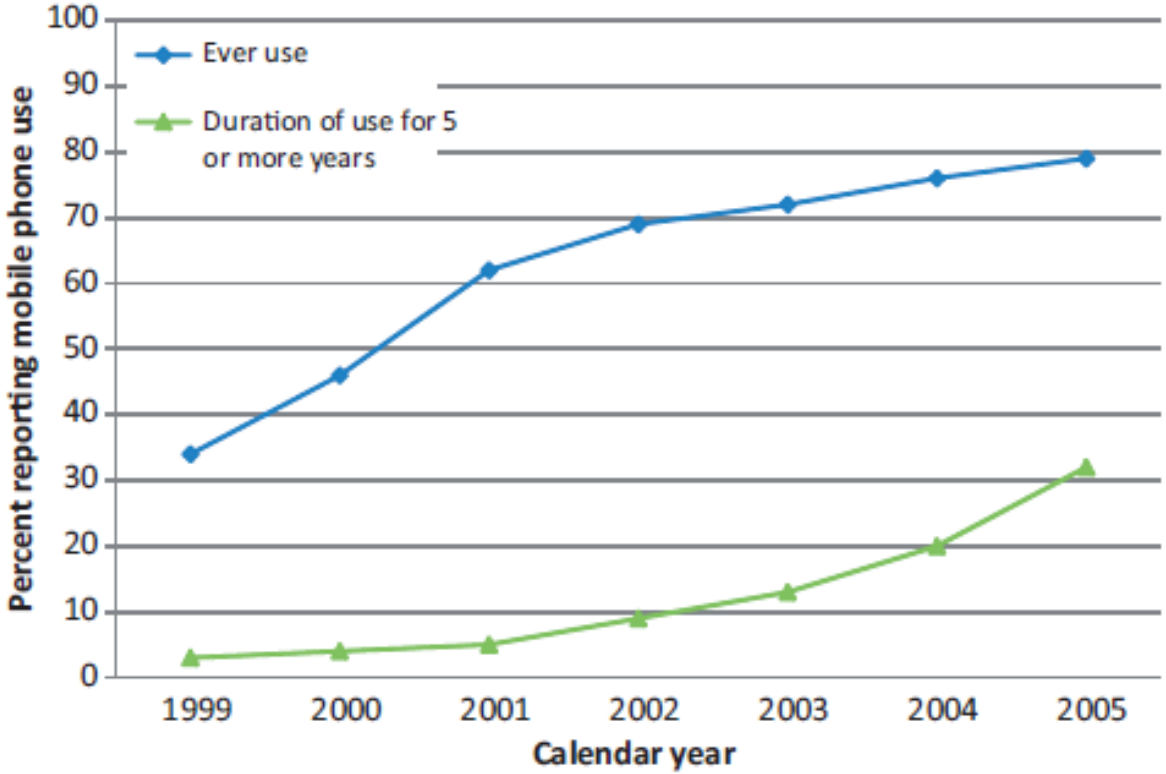



Frei P et al. *BMJ* 2011;343:bmj.d6387

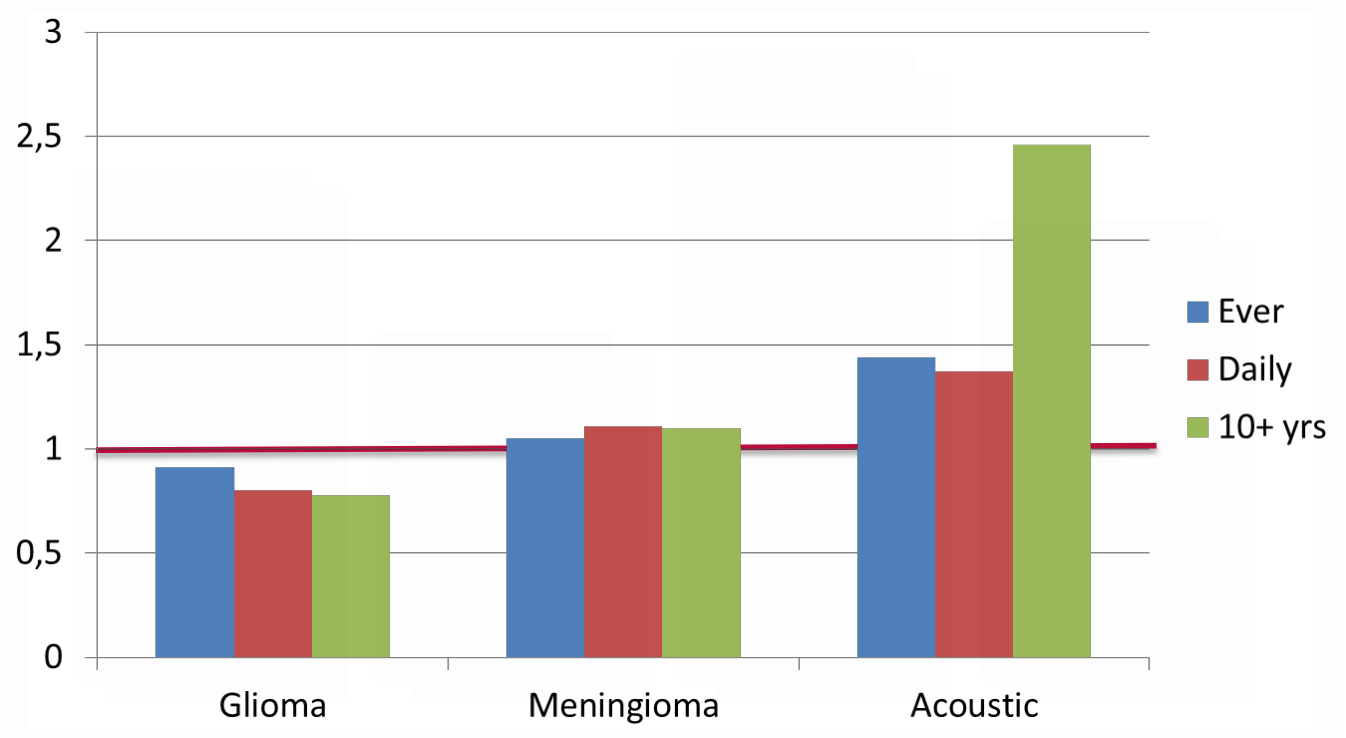
# UK cohort study – Million Women Study

- Benson et al. *Int J Epid* 2013
- 791,710 women recruited 1996-2001 at mammography screening
- Questionnaire for collection of exposure data
  - At baseline and a re-survey in 2009
  - 500,000 ever users and 300,000 never-users
- Follow-up on average for 7 years
  - 1261 incident cases

# Mobile phone use in the Million Women Study

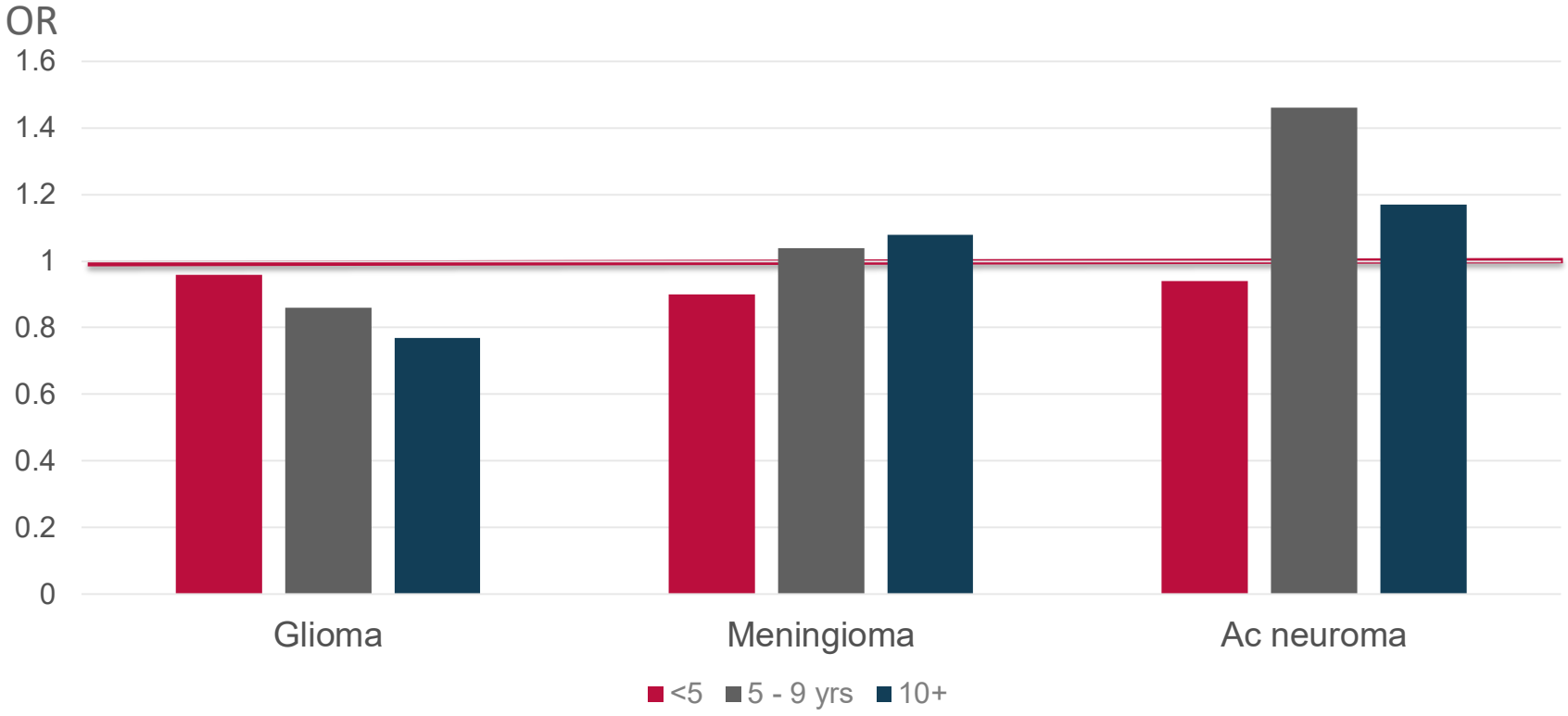


# Duration of use and risk of brain tumors




Benson et al. *Int J Epid* 2011

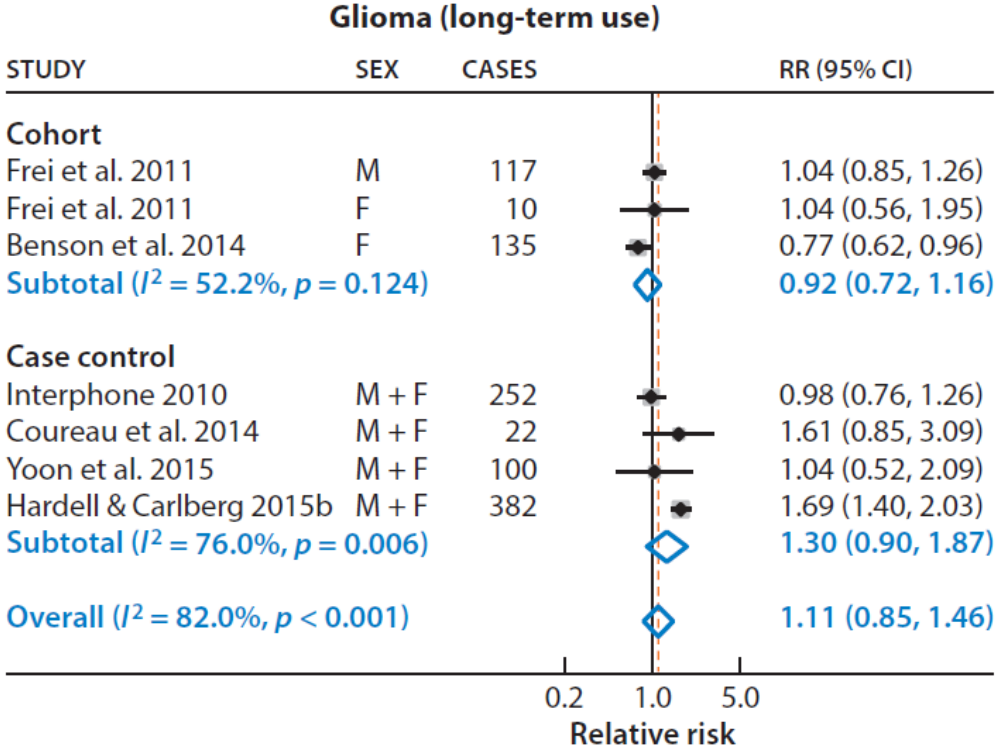
# Million women study extended follow-up (up to 2011)



# Meta-analyses of mobile phone use

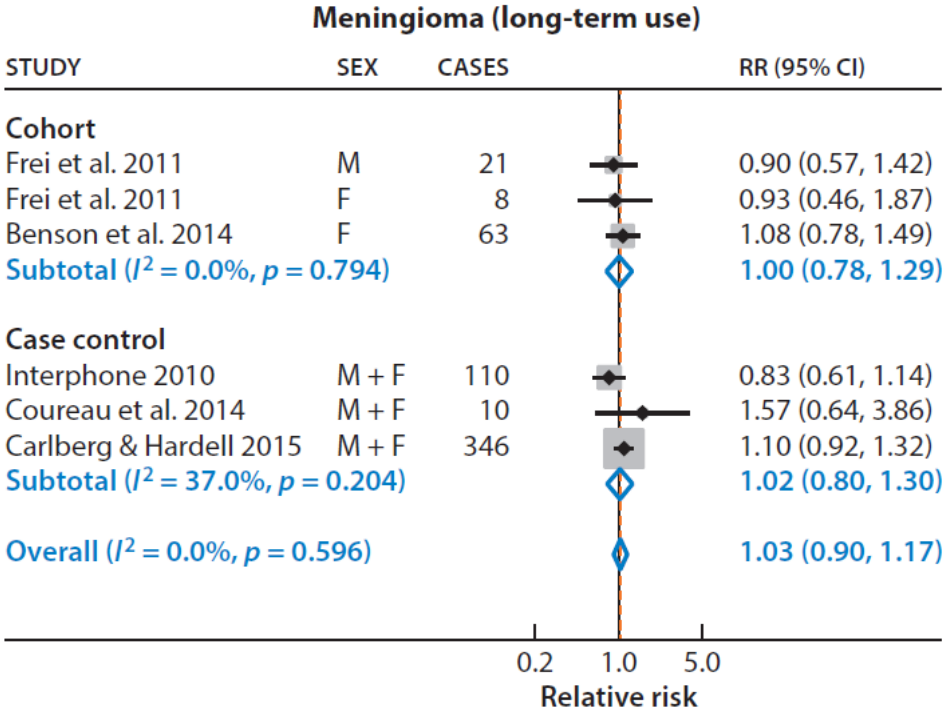
- Röösli et al. *Annu Rev Public Health* 2019: Focus on long-term use
  - ”Epidemiological studies do not suggest increased brain tumor risk with mobile phone use, although some uncertainty remains about long latency periods, rare subtypes and usage in childhood”
- Wang et al. *World Neurosurg* 2018: Wireless phone (DECT), glioma only
  - ”Ever use of wireless phones was not significantly associated with adult glioma, but there could be risk in long-term users”
- Bortkiewicz et al. *Int J Occup Med Environ Health* 2017: Overlap between studies??
  - ”The results support the hypothesis that longterm use of mobile phone increases risk of intracranial tumors, especially ipsilateral exposure”

# Meta-analysis - glioma



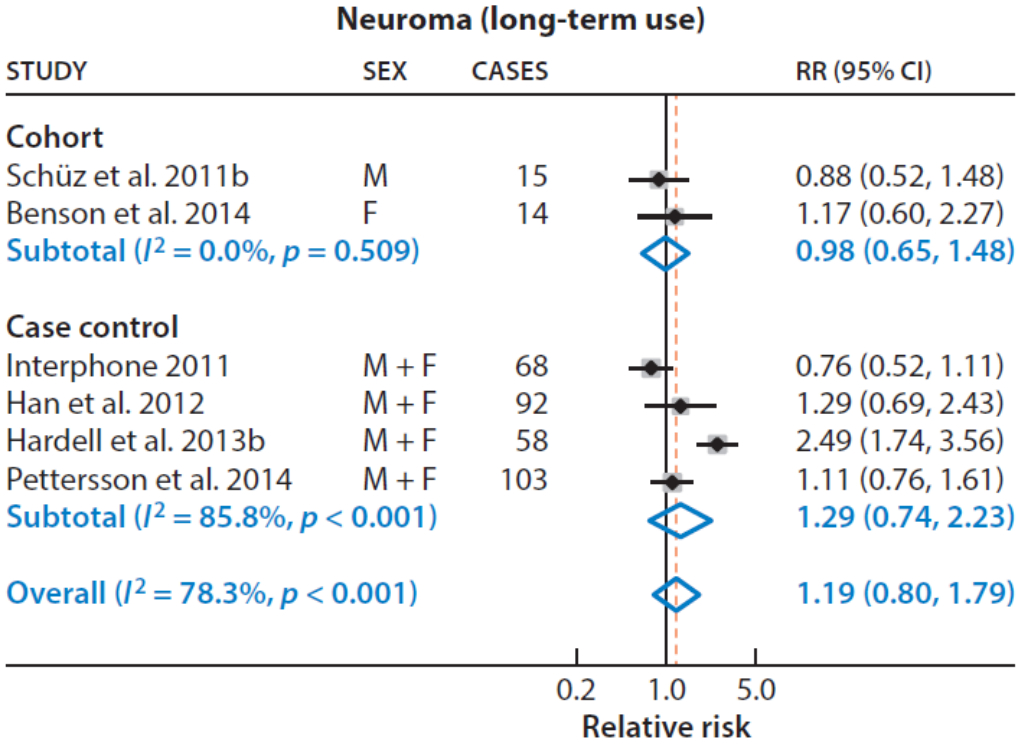

Röösli et al. 2019

# Meta-analysis - meningioma

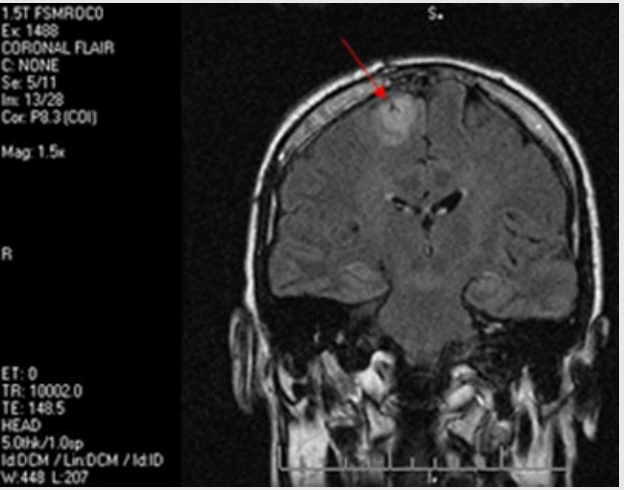



Röösli et al. 2019

# Meta-analysis – acoustic neuroma

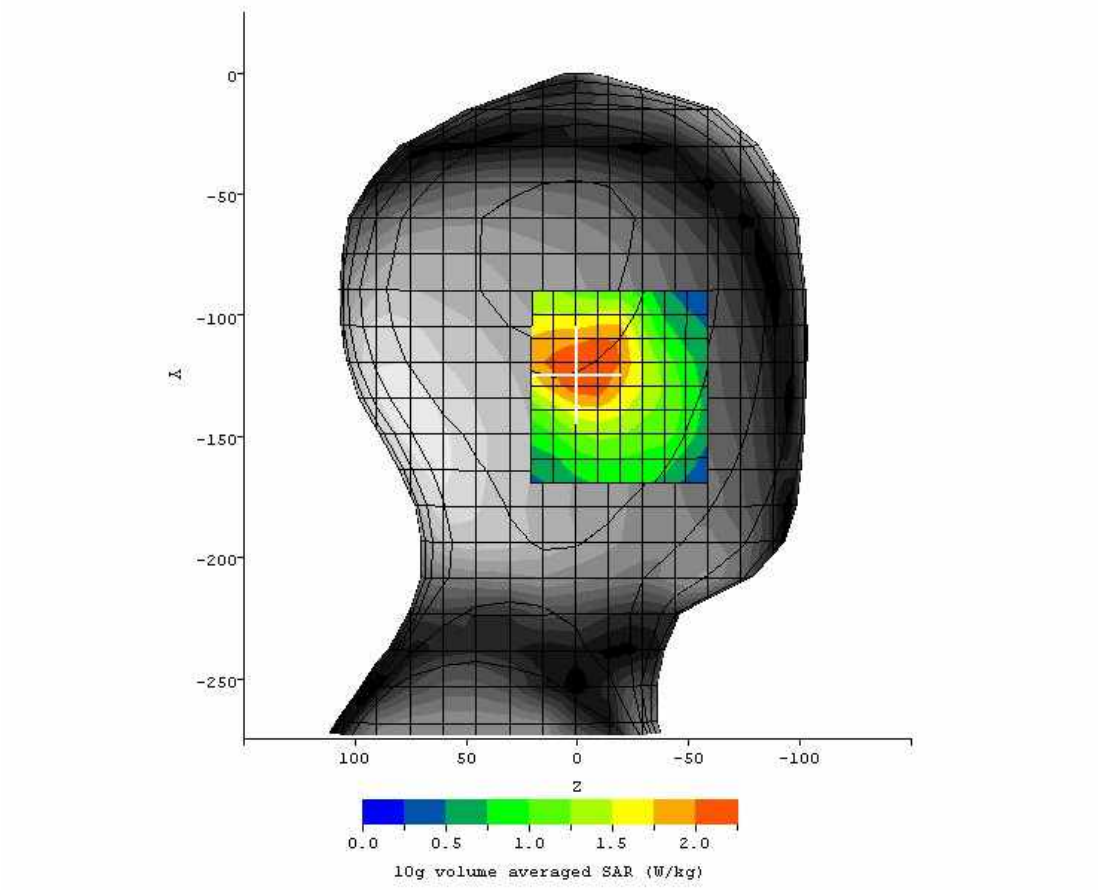



Röösli et al. 2019



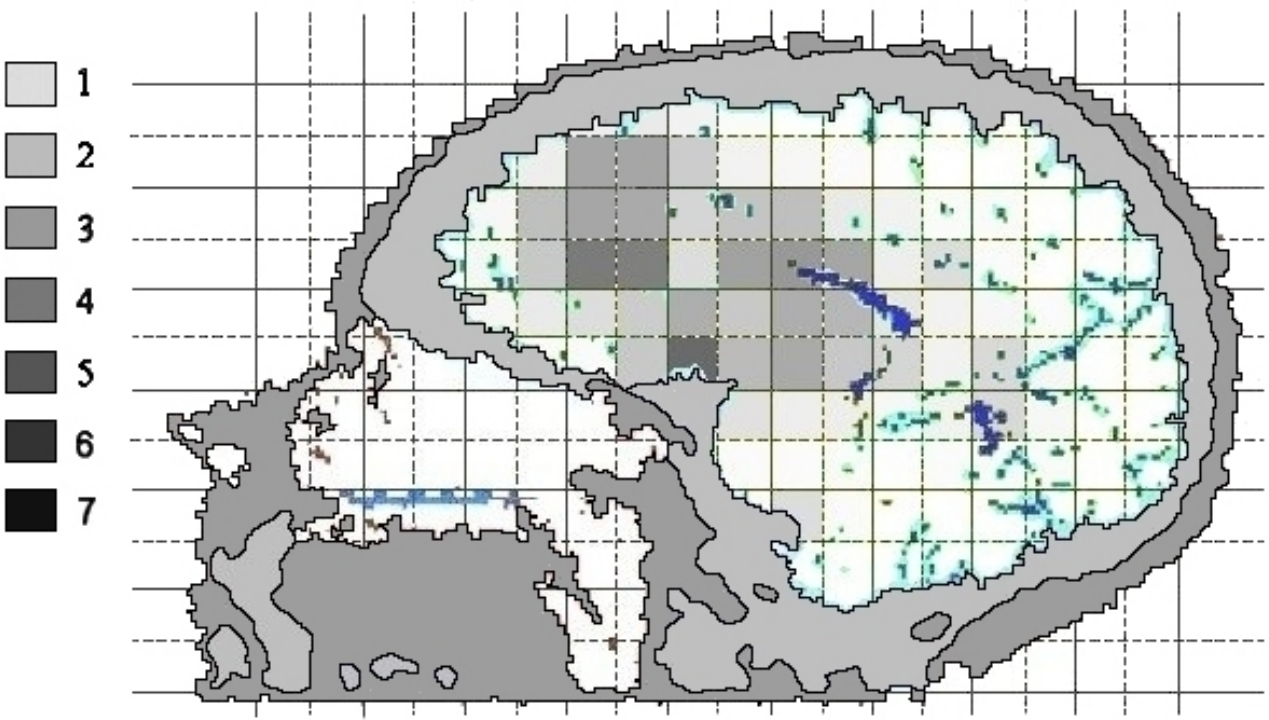

# Analyses of tumor location

# Local field – local effect?



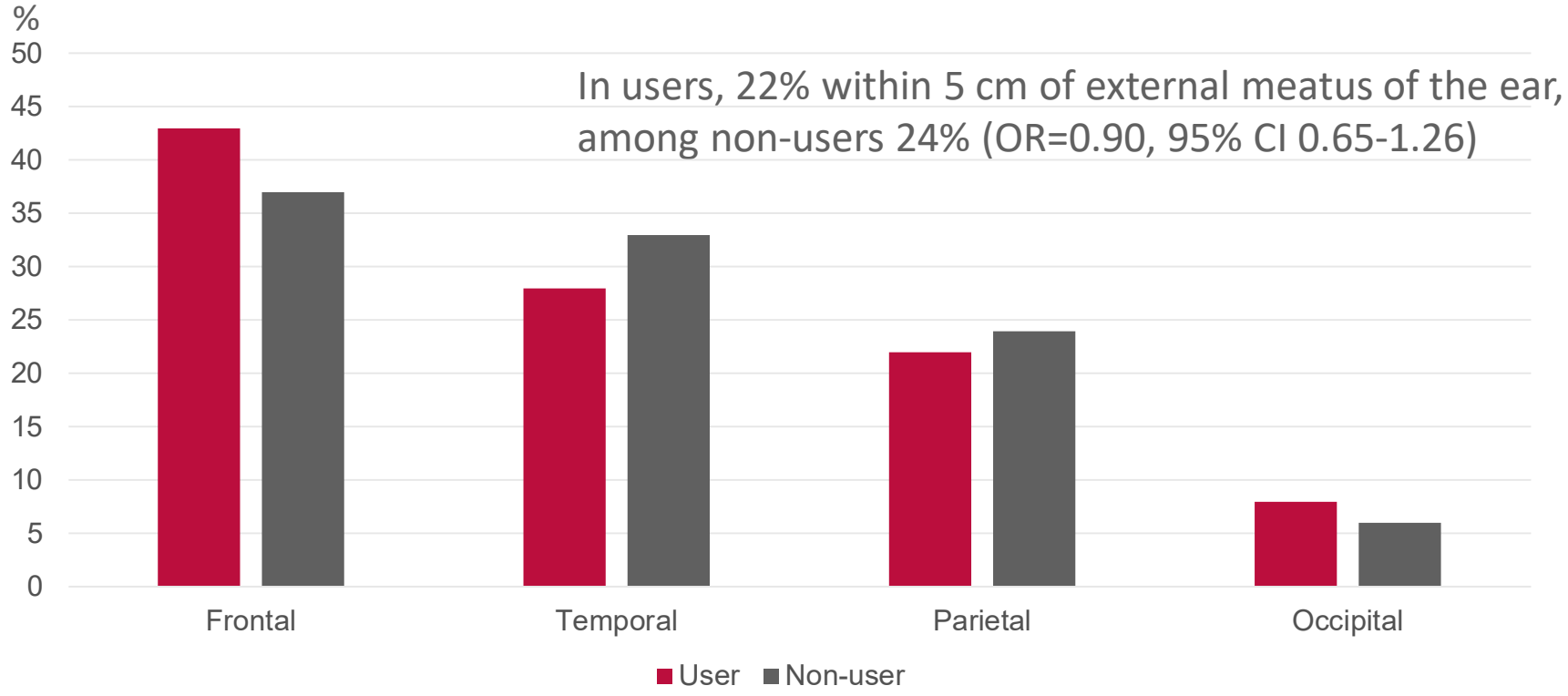
# Glioma location

888 cases from 7 Interphone centers



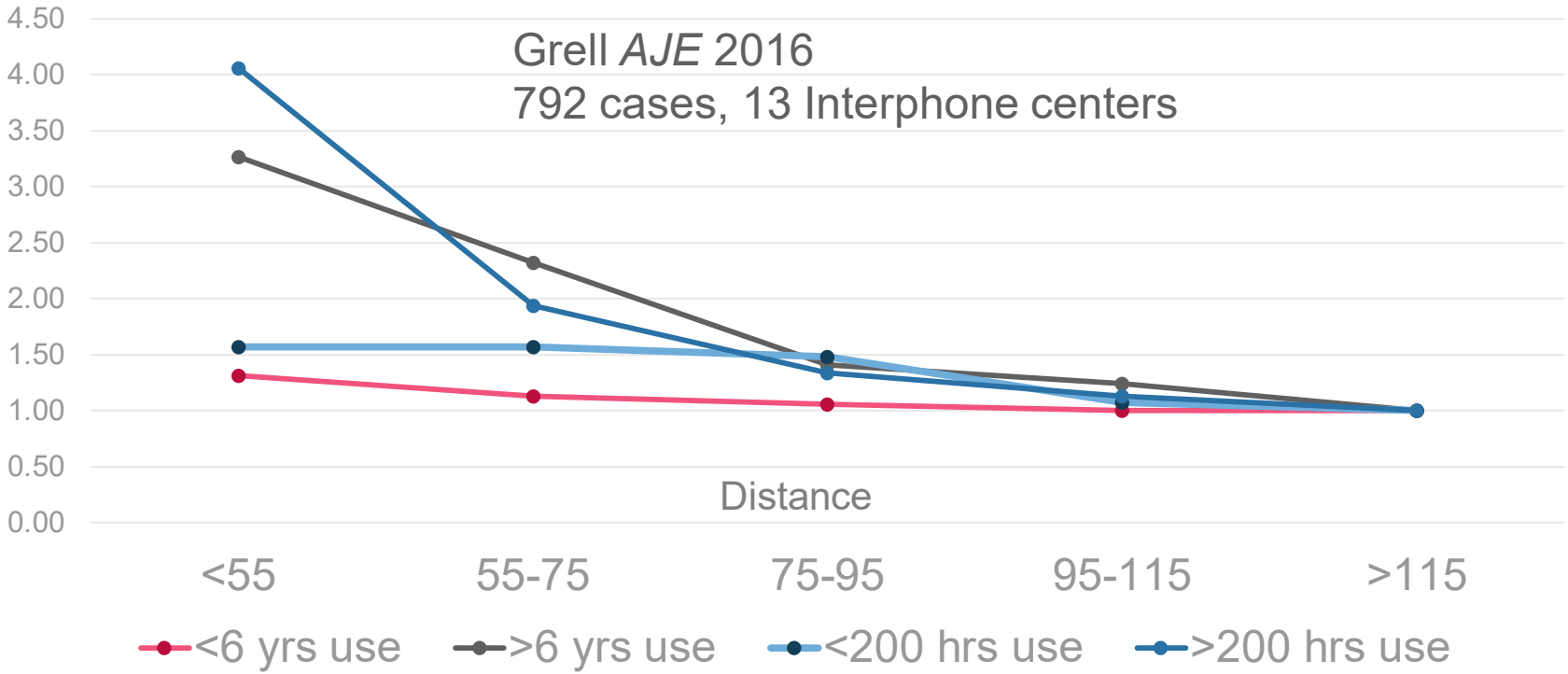

Larjavaara *Am J Epid* 2011

# Distribution of gliomas among cellular phone users vs non-users

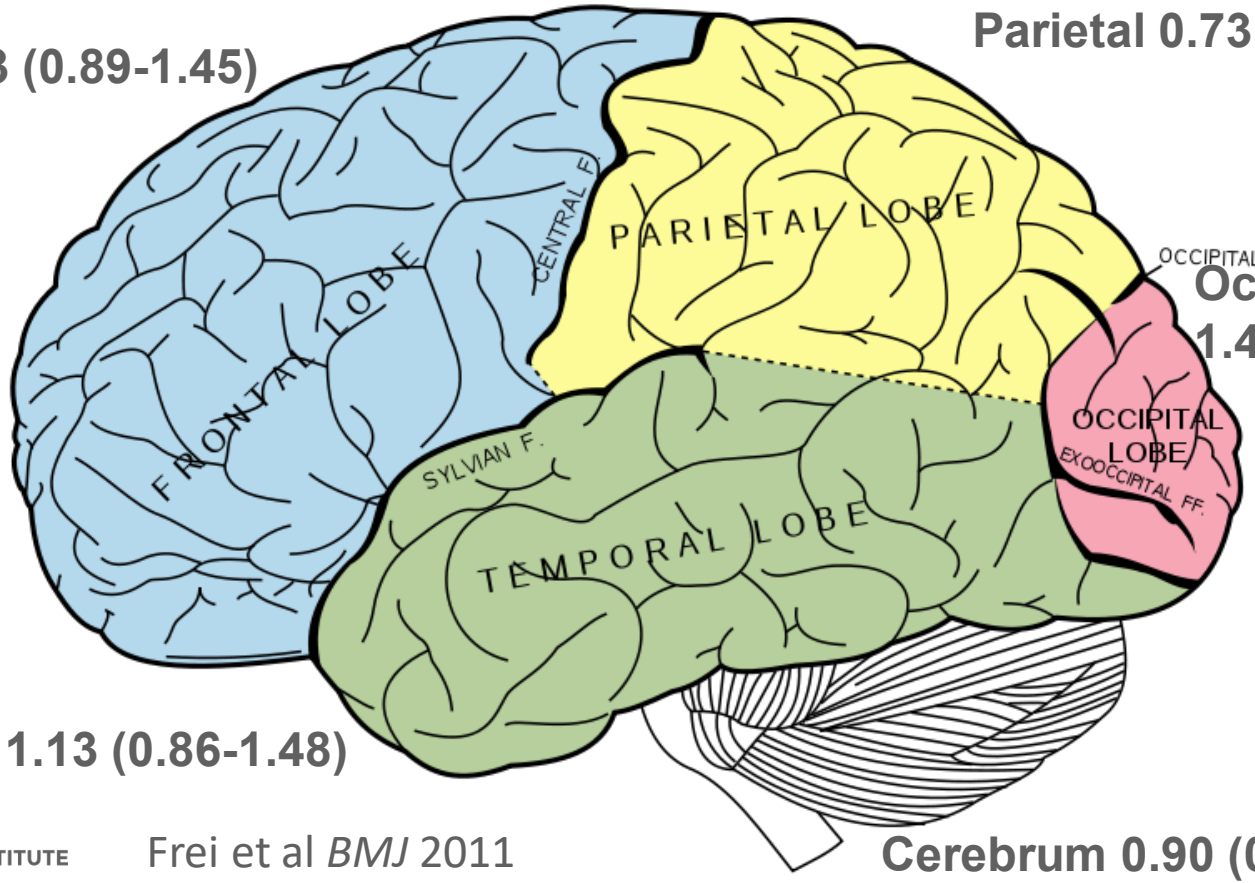



Larjavaara *Am J Epid* 2011

# Gloma location by cell phone usage



# Danish cohort: RR by location





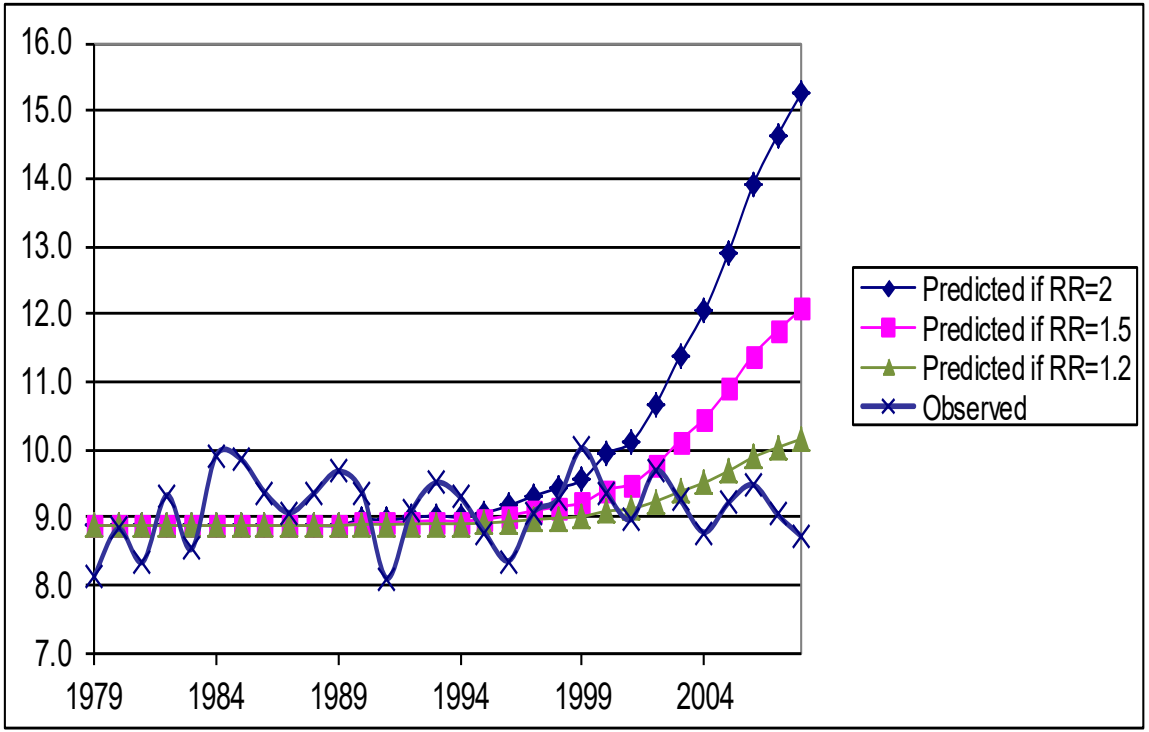

Frei et al *BMJ* 2011

# Incidence trends

# Reality check

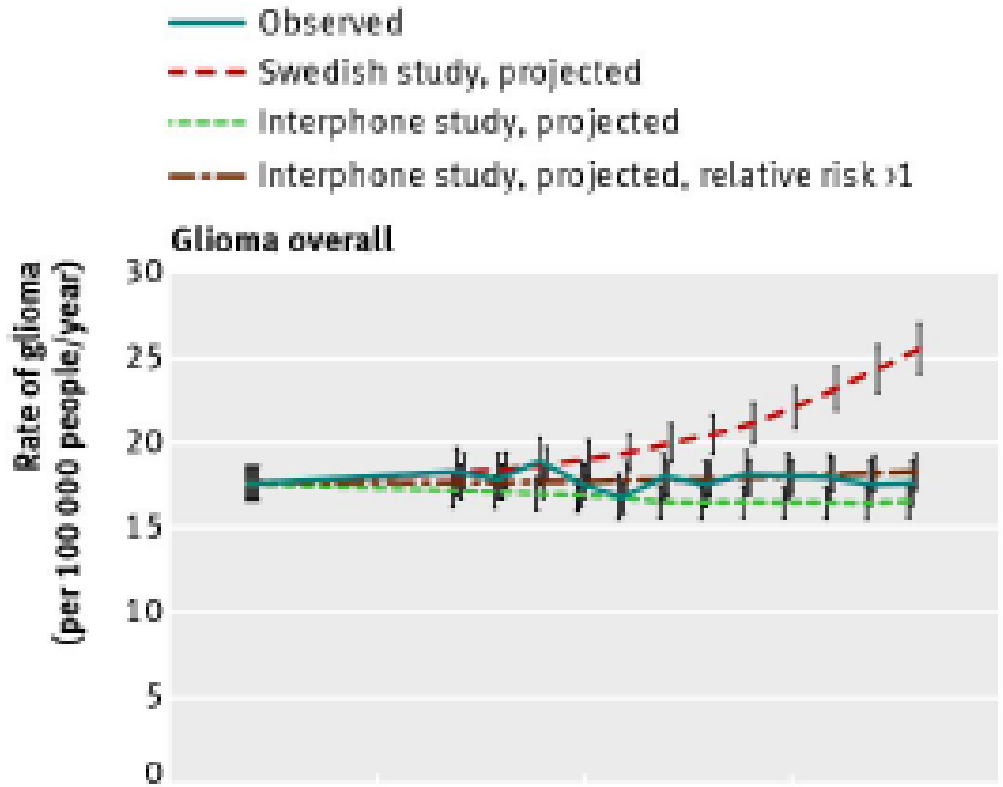
- If use of mobile phones increases brain tumor risk, we should be able to observe increasing trends in incidence at some point
  - Population coverage ~100%, widely adopted since late 1990's
- How large effect?
- What amount of cellular phone use?
- When does it occur (induction period or lag/latency)?

# Observed and predicted incidence, Nordic countries



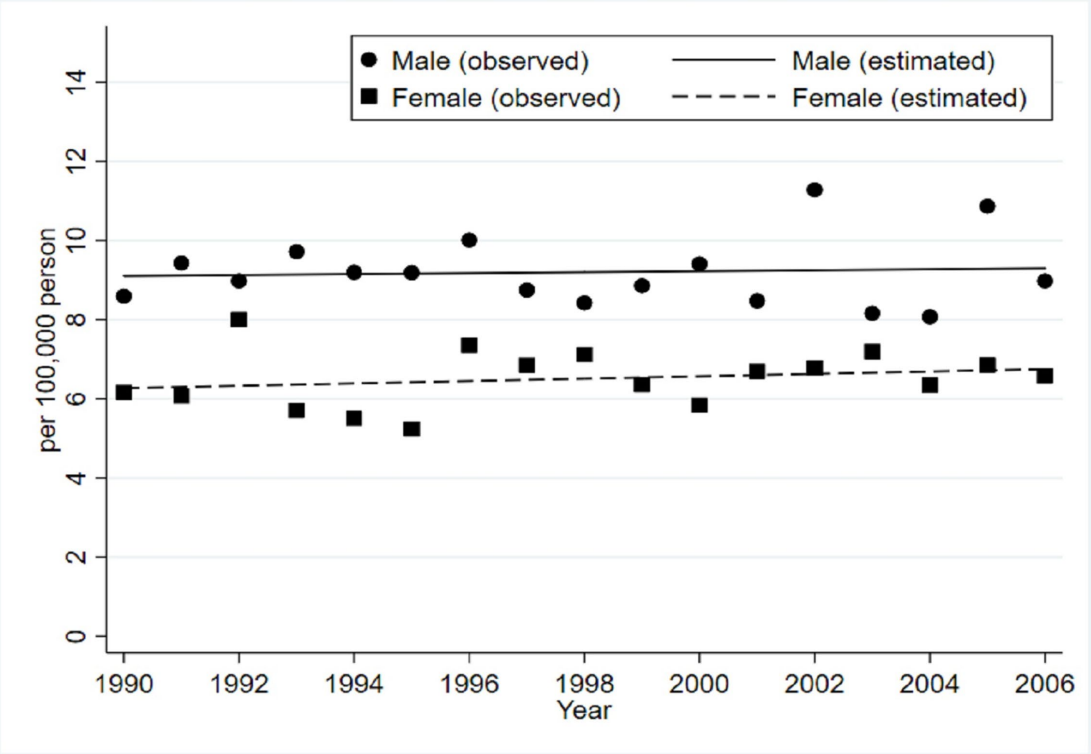

Deltour et al. *Epidemiology* 2012

# Observed and expected glioma incidence in the U.S.




Little et al. *BMJ* 2012

# Incidence of adult glioma in Finland



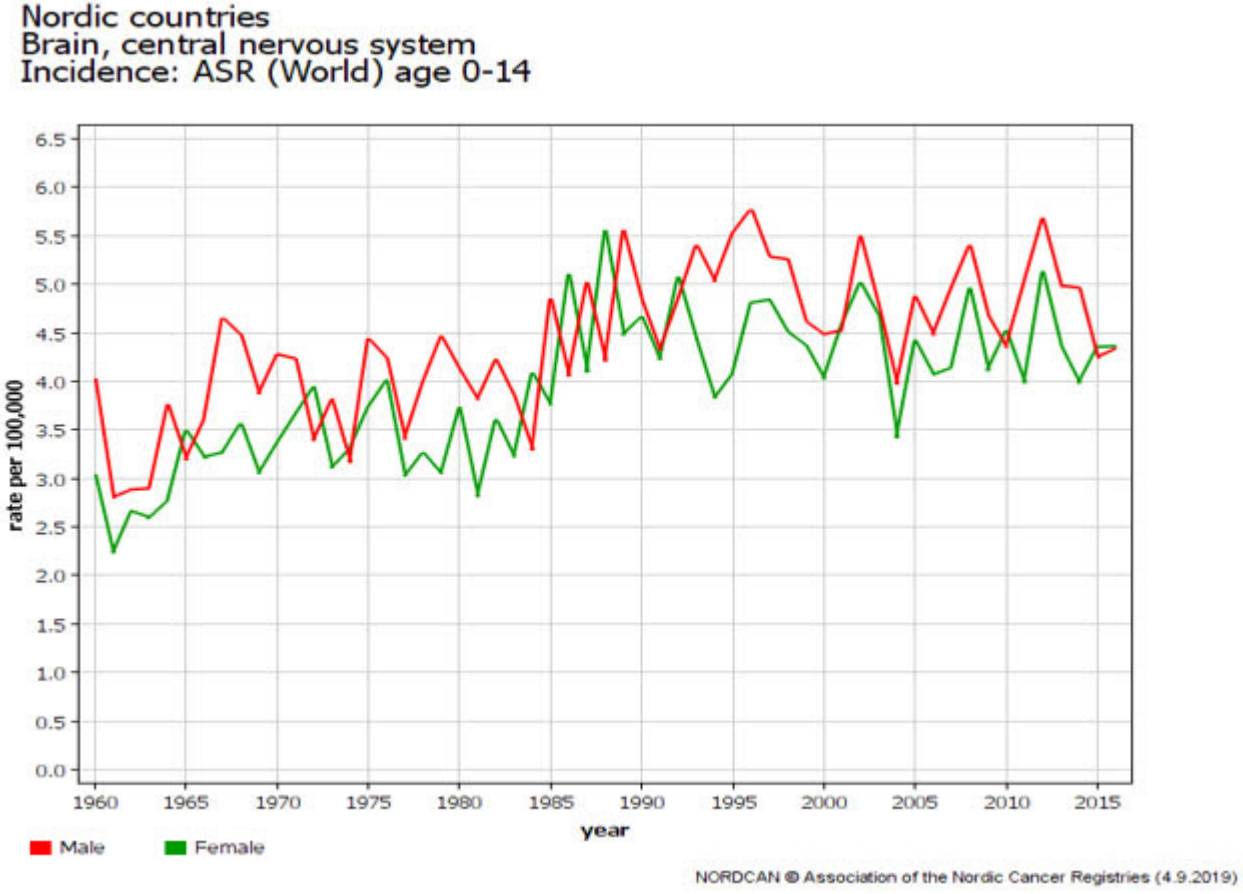

**Incidence 7.7/100,000**
Men: 9.3, women: 6.5

**No obvious trend**
APC: +0.1% (95% CI: -0.5, +0.7)
For 2007-2016, APC -0.5%

For temporal tumors,
APC -0.6% (-1.8, +0.5)

Natukka et al. *Acta Oncol* 2019

# Latest incidence trends, children, Nordic countries



# Summary and conclusions

# IARC carcinogenicity review

- Radiofrequency EMF classified in 2102 as 2B – possibly carcinogenic to humans
  - Limited evidence in humans and experimental animals
  - Similar assessment as for ELF-EMF
- Based on epidemiological studies of glioma and acoustic neuroma
  - Interphone: Highest amount of cumulative use, ipsilateral use, temporal lobe tumors
  - Hardell studies and a Japanese case-control study
- Minority opinion suggested ‘inadequate evidence’ due to null findings in cohort studies and temporal trends

# Summary

- Case-control studies have not shown strong evidence for increased brain tumor risk in relation to mobile phone use
  - Some indications of increased risk, but with an inconsistent pattern
  - Location of gliomas not affected by mobile phone use, though some discrepancy in results
- Real world data do not show increases in brain tumor incidence trends <20 years after large-scale adoption of mobile phones
- Cohort studies show little indication of increased risks
  - COSMOS substantially larger, with quantitative call-time data
- There are still uncertainties but the balance of evidence post-IARC weighs toward no major health impact

# Developments awaited

- MobiKids study
- COSMOS Cohort Study of Mobile Phone Use and Health
  - Swe-Fin-Den-UK-NL-Fra
  - 260,000 participants
  - Follow-up from 2009-2010
  - Analyses of tumor risks pending
- IARC carcinogenicity review to be revised

# ICNIRP summary

- Extensive research has been undertaken in relation to exposure to HF fields used specifically in mobile telephony
- Risk of tumors in close proximity to the ear where the phone is held, e.g. brain tumors, has been a key focus, some studies reporting a slight increase in risk for long-term and heavy mobile phone users
- Reporting biases and weaknesses of the studies may explain the observed findings.
- Several studies have not reported any increase in brain tumors with mobile phone use
- The increased risk observed in some of the epidemiological studies is inconsistent with the stable frequency of occurrence of these cancers in the population
- ***The overall evaluation of all the research on HF fields leads to the conclusion that HF exposure below the thermal threshold is unlikely to be associated with adverse health effects***

# Quiz (1)

**Exposure assessment in studies of cancer risk associated with mobile phone use need to overcome methodological challenges related to:**

A. Recall bias

B. Random error/misclassification in self-reported usage

C. Lack of a physical dose concept

D. All of the above

# Quiz (1)

**Exposure assessment in studies of cancer risk associated with mobile phone use need to overcome methodological challenges related to:**

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# Quiz (2)

**Evidence supporting an increased risk of brain tumors is mainly**

A. Increasing incidence trends

B. Positive results from cohort studies

C. Increased risks found for meningioma

D. None of the above

# Quiz (2)

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U.S. Department of Health & Human Services

National Institutes of Health | National Cancer Institute

dceg.cancer.gov/

1-800-4-CANCER

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