Mobile phones and cancer – what has epidemiology found

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Studies of mobile phones and cancer

- Focus has been on tumors in the head and neck region
- Mostly brain tumors
  - → Glioma, meningioma, acoustic neuroma
- A few studies on parotid gland tumors
- Single studies on uveal melanoma, lymphoma, other tumors

Brain tumors

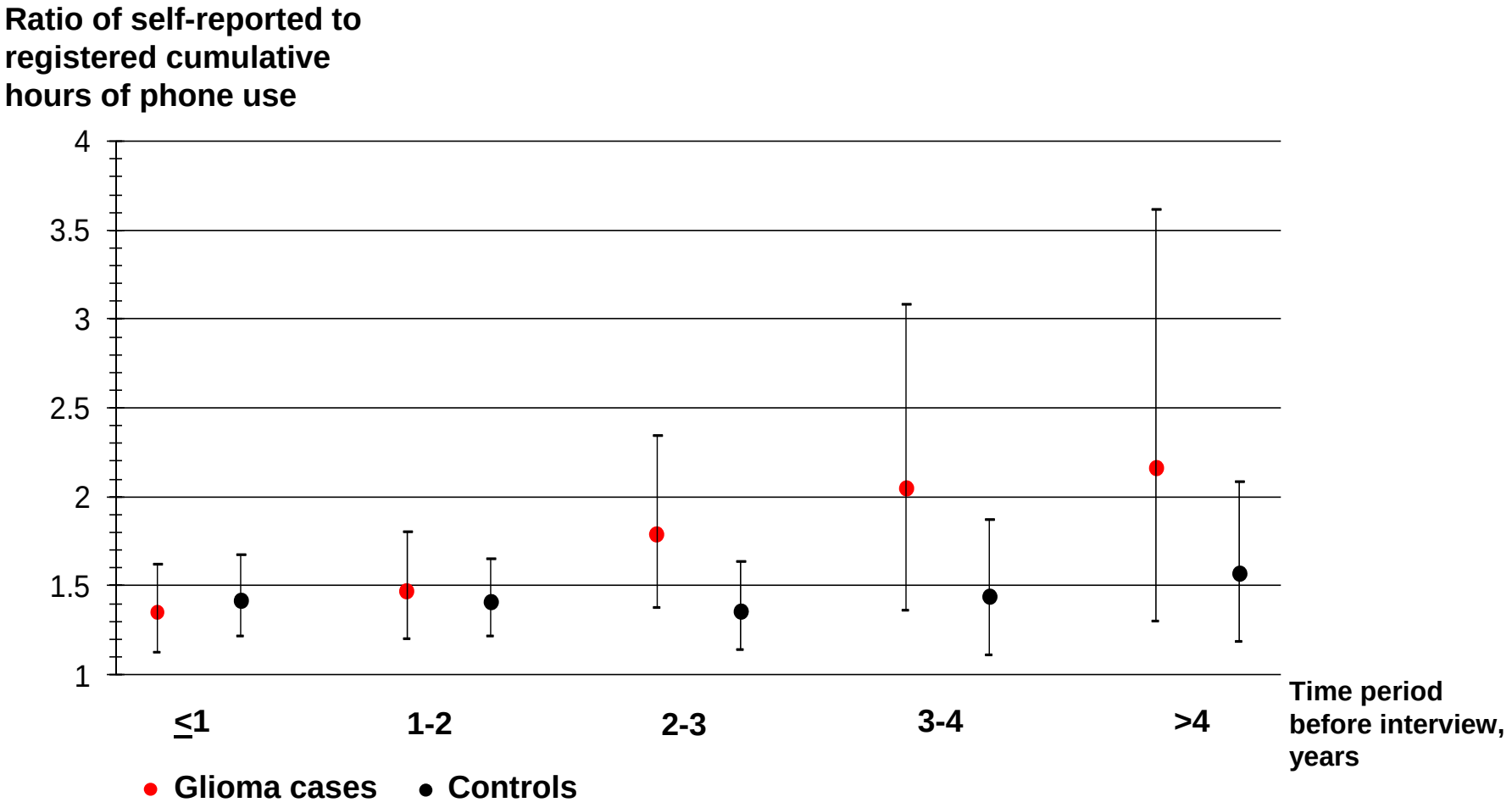
- ~15 published studies available on brain tumors and mobile phone use, and slightly fewer on acoustic neuroma

- Four groups of studies:
  - → Early US-studies
    - Short duration of use
  - → Hardell et al.: 3 studies from Sweden
  - → Interphone studies: international collaborative studies performed in 13 countries with a common protocol
  - → Nordic registry based studies (subscriber data)

Methodological issues – exposure assessment

- Register based exposure information
  - → Non-differential exposure misclassification
    - The subscriber is not necessarily the user of the phone
    - Corporate users difficult to identify
- Self-reported exposure
  - → Non-differential exposure misclassification – difficult to remember mobile phone use many years in the past
    - Heavy users tend to overestimate mobile phone use and light users tend to underestimate
    - Can lead to underestimated effects
  - → Recall bias
    - Glioma cases overestimate exposure in distant past – can lead to overestimated risk estimates

Interphone validation study



Methodological issues – selection bias

Non-participation – potential selection bias

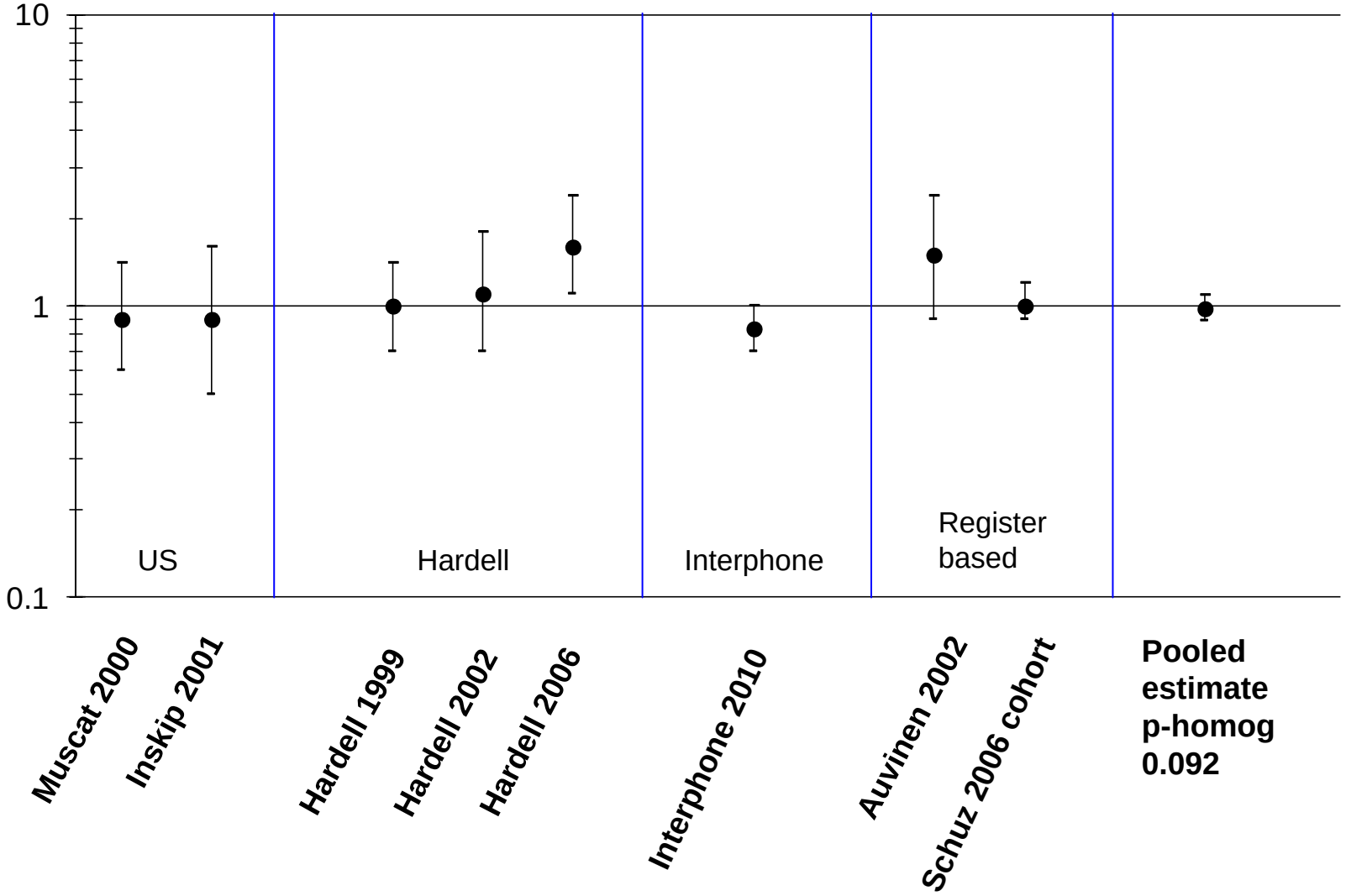
→ Mobile phone users more likely to participate

Prevalence of ever mobile phone use in Interphone:

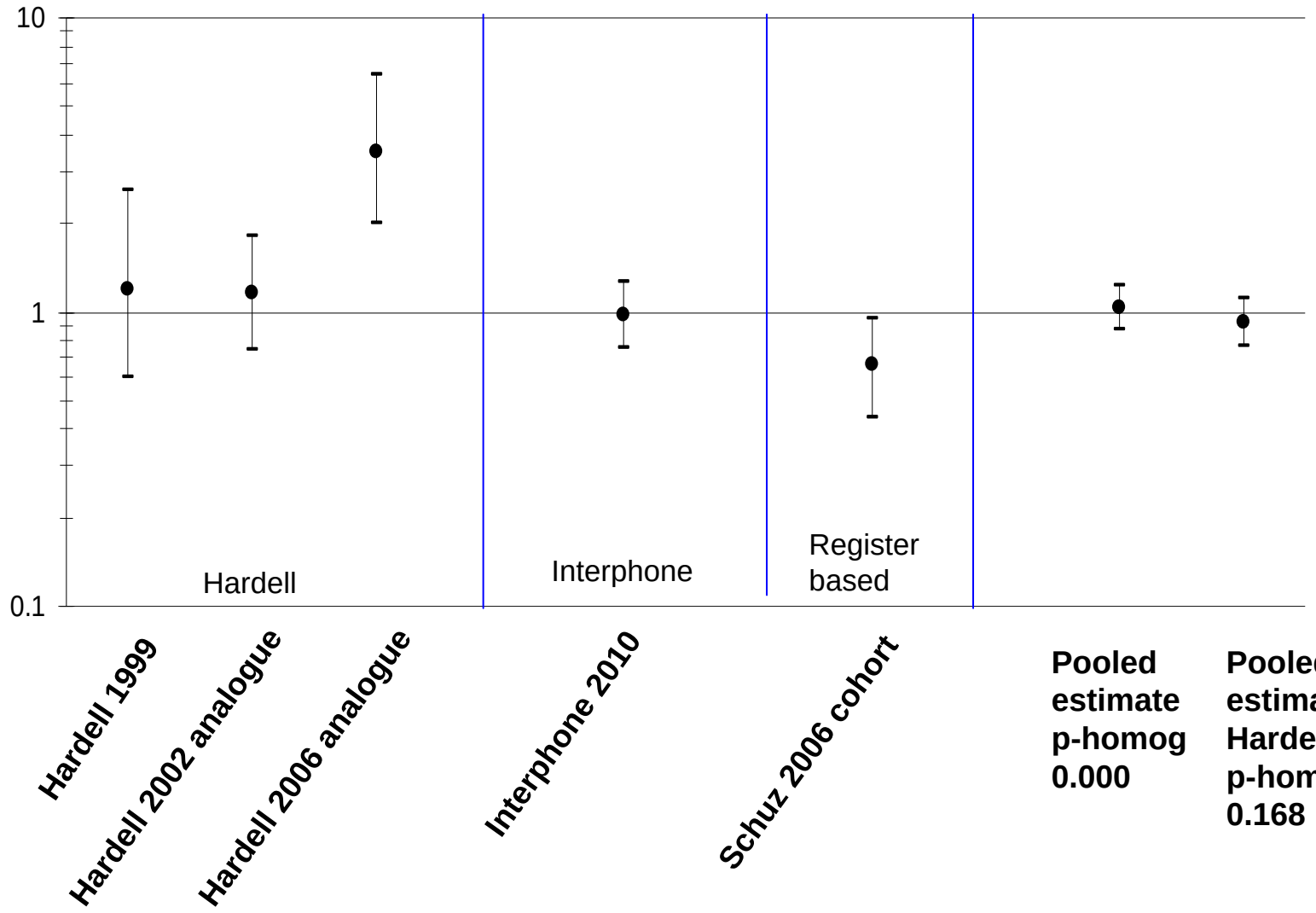
	Refusers	Participants
Controls	56%	69%
Cases	50%	66%

- Leads to underestimation of risk estimates by approx. 10%

Time since first use, regardless of amount of use: Glioma and mobile phone use, **short** latency period (~ <5 years)



All studies: Glioma and mobile phone use, **long** induction period, ~ ≥ 10 years



Danish mobile phone subscribers cohort

- Results for glioma:
  - → **First analysis** (i.e. short-term use): RR=0.94 (0.72-1.20)
    (Johansen 2001)
  - → **Update** (short to intermediate-term use): RR=1.01 (0.89-1.14)
    (Schuz 2006) 5-9 years: RR=0.96 (0.84-1.09)
    10+ years: RR=0.66 (0.44-0.95)
  - → **Second update** (long-term, use)
    (Frei et al 2011) 10-12 years: RR=1.06 (0.85-1.34)
    ≥13 years: RR=0.98 (0.70-1.36)

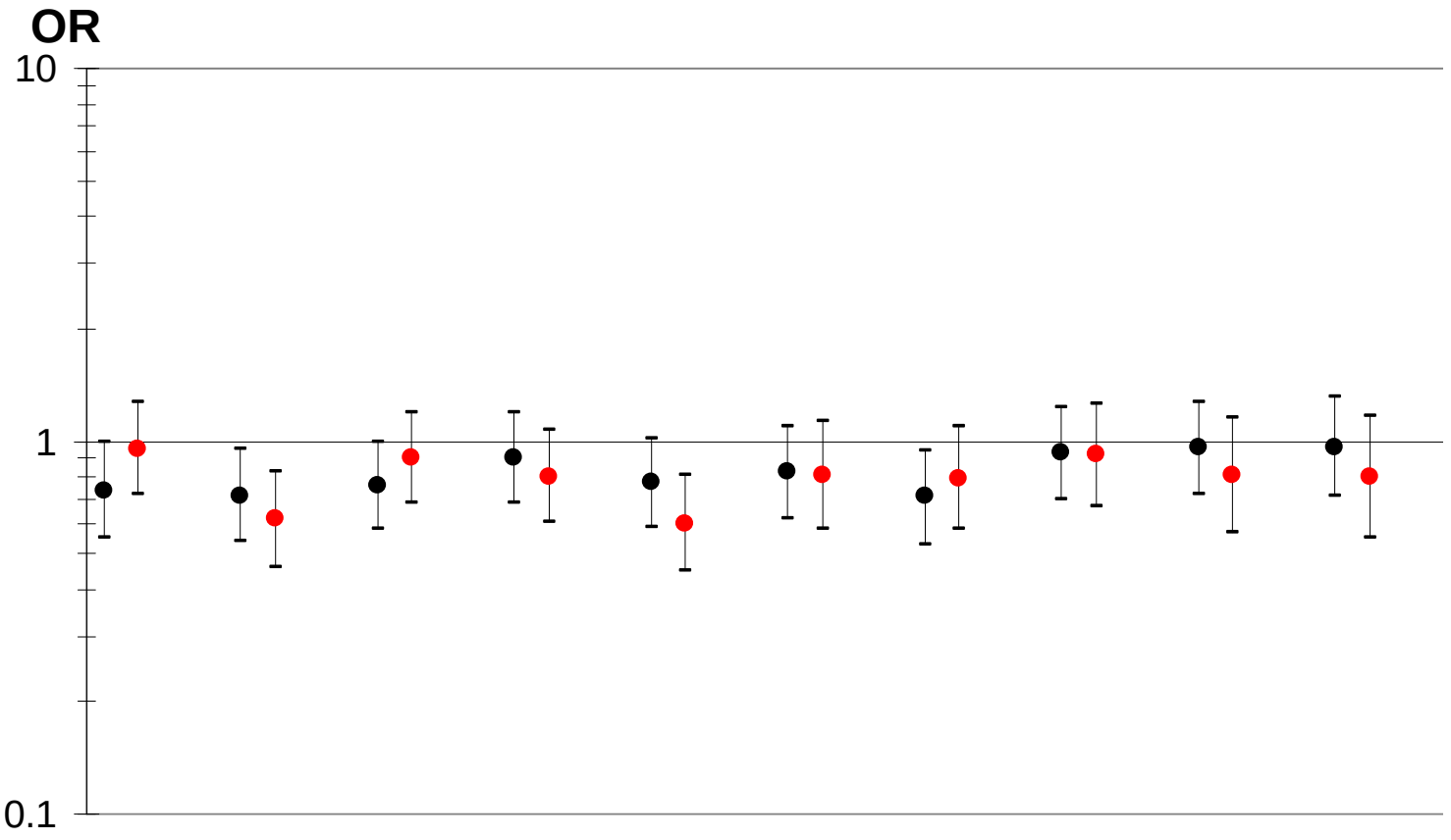
Incidence trends strongly support absence of short- and intermediate-term effect

Exposure misclassification, Danish cohort study

Assume that the true relative risk is 2.5

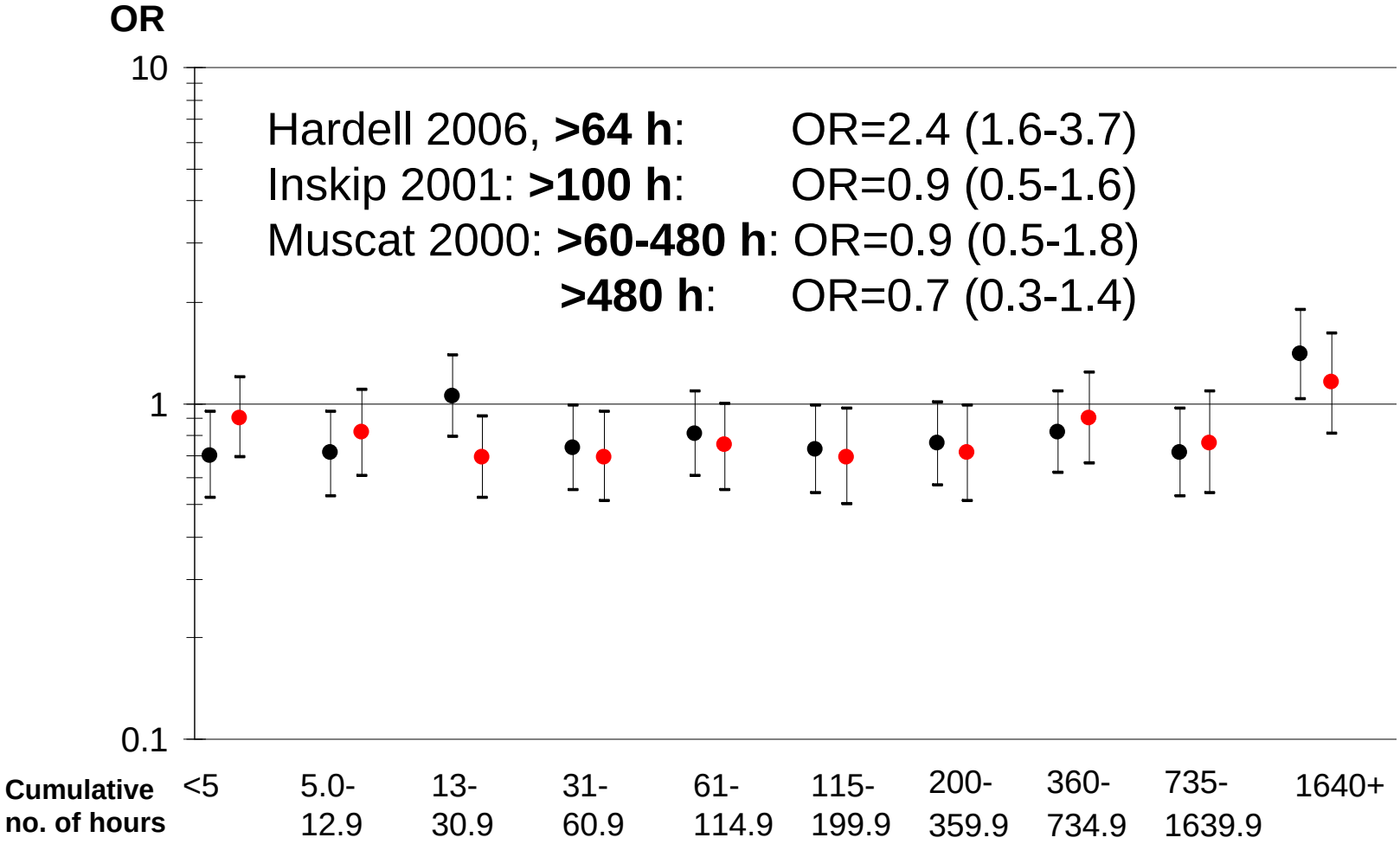
Adding 300,000 subscribers to unexposed results in a RR of 2.23

Amount of use Interphone, glioma: Cumulative number of calls



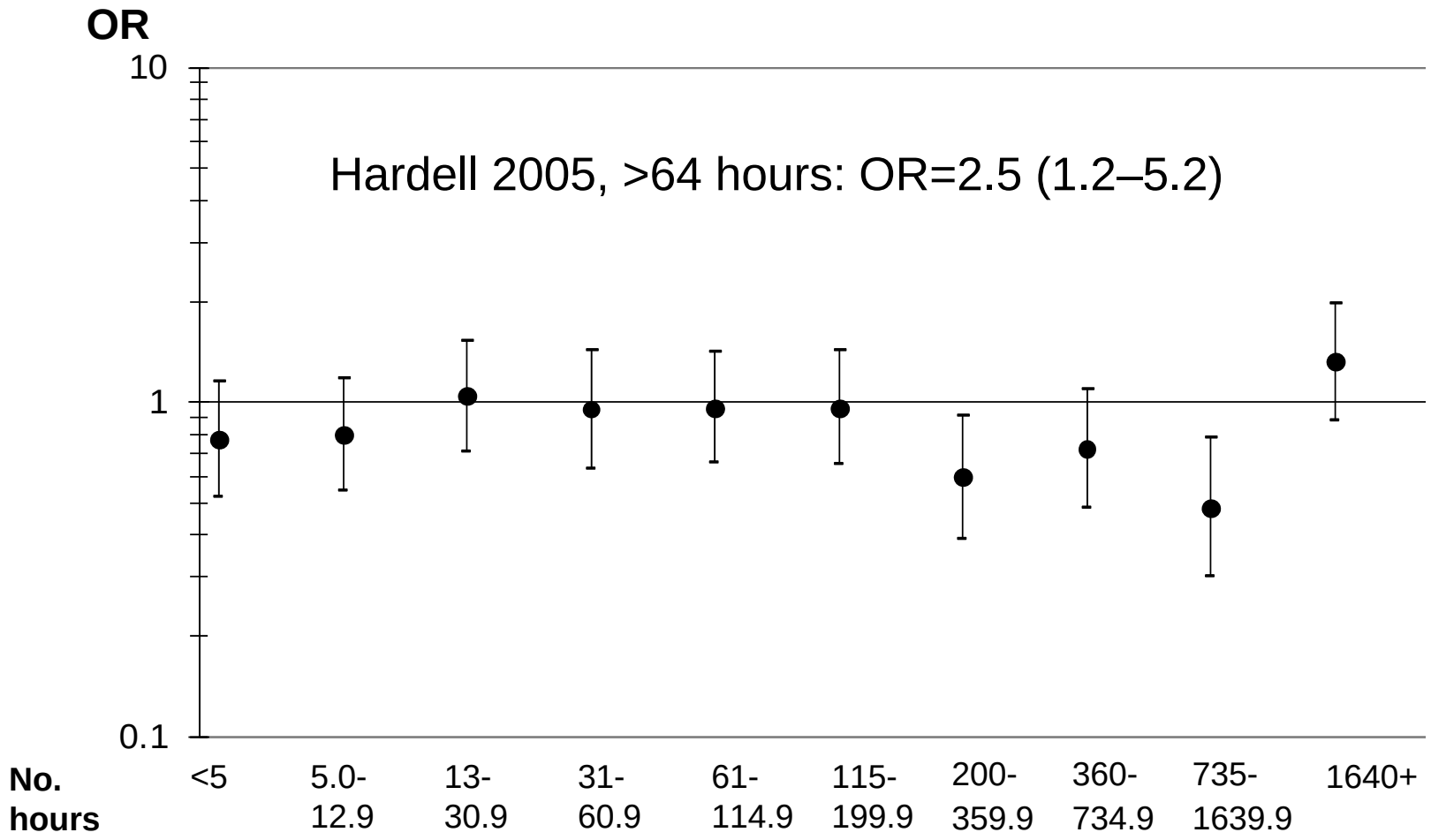
- **Glioma**
- **Meningioma**

Interphone results, glioma: Cumulative call duration



- **Glioma**
- **Meningioma**

Interphone results acoustic neuroma:
Cumulative hours of use



Comments

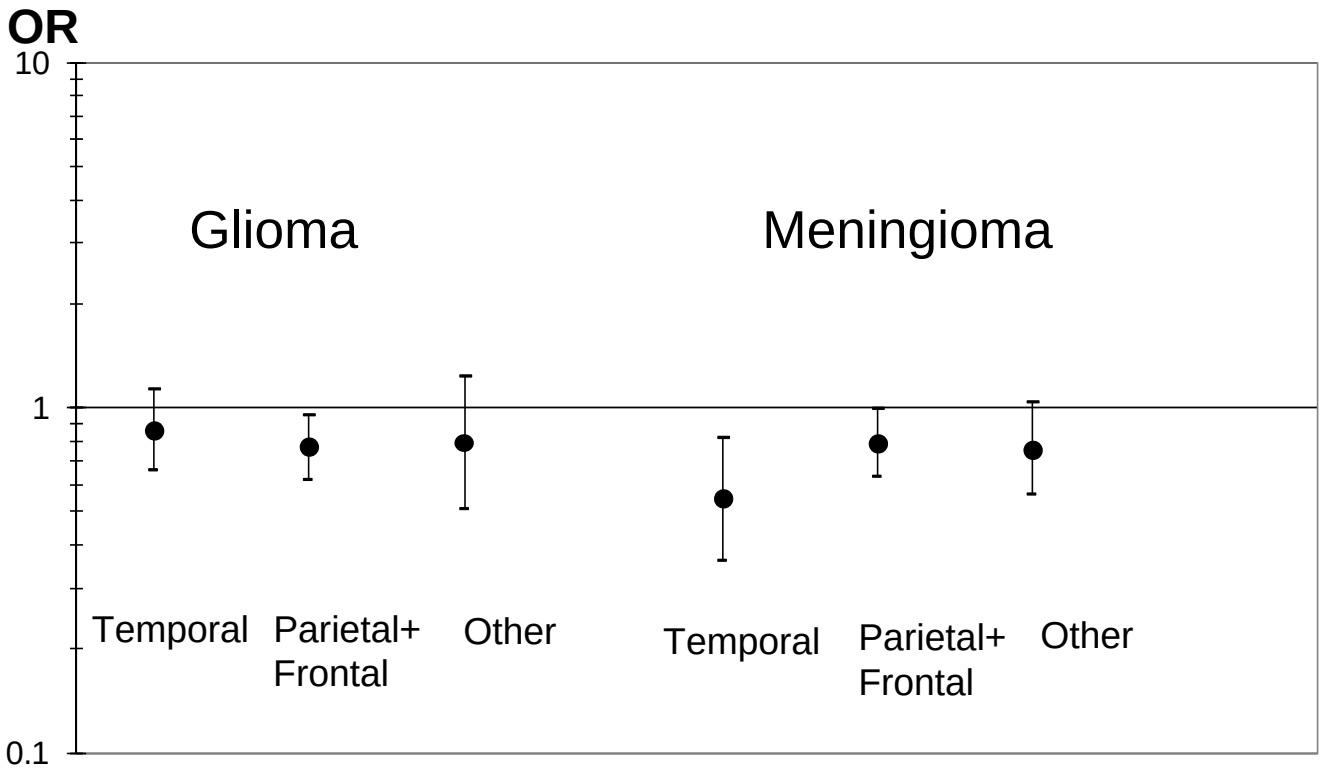
- Does the increased risk of glioma in the most extreme usage category, >1640 h, reflect causality?
  - → There are persons in this category who reports highly implausible call times, more cases than controls
    - e.g. more than 12 hours per day, everyday during many years
  - → Validation study of self reported hours of use found that cases overestimate their use more for distant periods than controls
  - → No increased risk in relation to cumulative number of calls
    - High correlation between number of calls and duration of calls when analysed in independent sample (Spearman= 0.94, Swedish COSMOS, unpublished data)
  - → No dose-response: No risk increase in first nine exposure categories – elevated risk only in the most extreme category

Laterality of phone use vs tumor

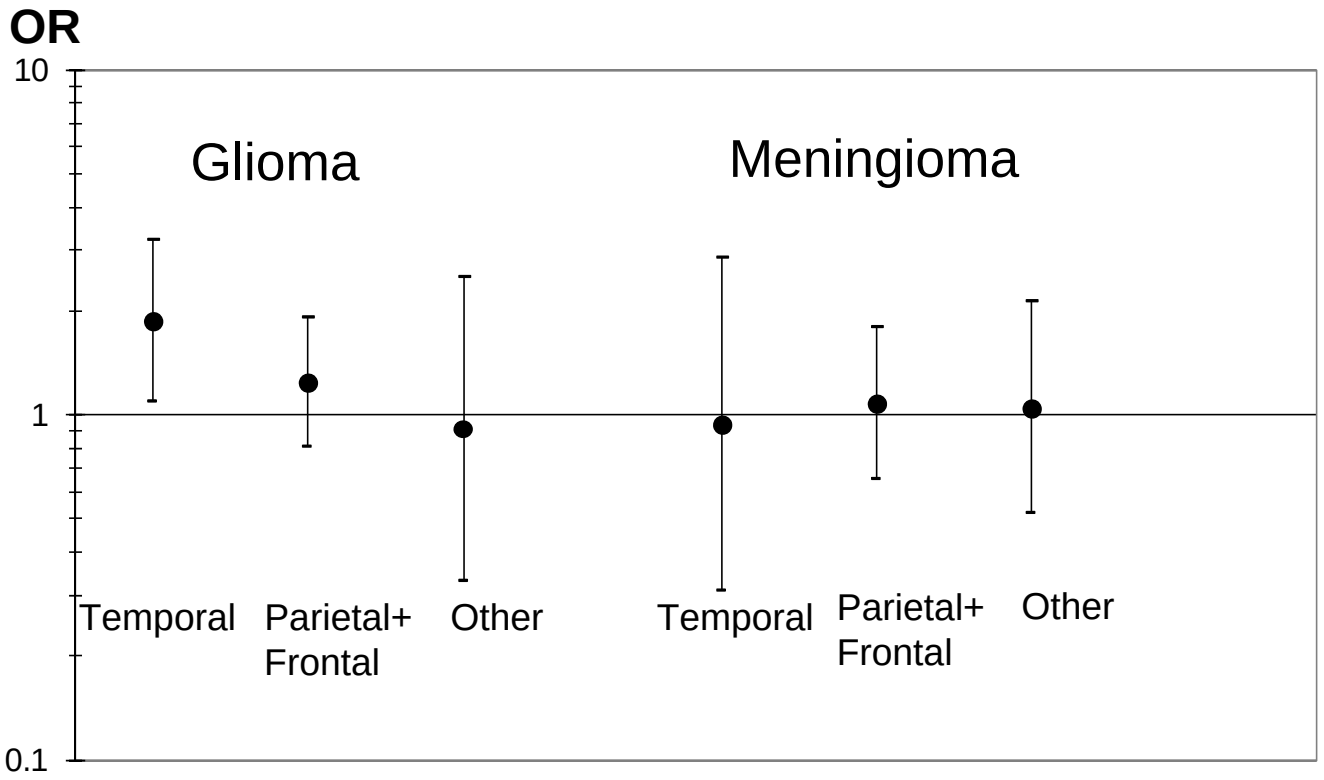
- For causality one would expect
  - → For short term use, short duration of use, few phone calls: Risk should be the same as for unexposed subjects, i.e. estimates close to unity for both ipsi- and contralateral use
  - → For long term use, long duration, many calls: Increased risk on same side; for opposite side, risk should be the same as for unexposed subjects, i.e. close to unity

- **Interphone found:** Higher risk estimates for mobile phone use on the same side as the tumor in **virtually all** exposure categories
  - → Often strong protective effect on opposite side of the head
  - → Highest ratio of ipsi- to contralateral use among subjects with less than 2 years of mobile phone use and shortest duration of calls
  - → **Indicates recall bias when reporting side of use**

Lobe specific results Interphone: Ever regular mobile phone use



Lobe specific results Interphone: ≥1640 h of cumulative use



No other study reports higher risk for glioma in the temporal lobe

Localization of the tumor in the brain; case-case analyses in 7 countries

- RF from mobile phone highly localized – most of the exposure absorbed within a few centimeters
- Hypothesis: gliomas in mobile phone users are located closer to the exposure source (i.e. position of the handset) than gliomas in non-users
- Case-case analyses avoids selection bias

  → Included 888 glioma cases

- Results: glioma in mobile phone users were **not** preferentially located in highly exposed areas of the brain

Larjavaara et al. 2011, AJE

Cardis et al., 2011, estimate of RF energy

Results for top quintile	Complete data	Tumor centre by neurorad. or estimated	Tumor centre by neuroradiologist
Hour of use	**1.17 (0.88-1.56)**	1.25 (0.88-1.77)	1.72 (1.07-2.77)
RF energy		1.35 (0.96-1.90)	1.66 (1.03-2.67)
RF energy excl. information on side of head		**1.21 (0.87-1.68)**	Not reported

- If RF exposure was causally related to glioma:
  - → Stronger risk estimates would have been expected based on estimated RF energy, than on simply self reported hours of use
    - Almost identical risk estimates when removing info on side of head
- **Estimated RF energy seem to rely heavily on self-reported hours of use and side of phone use, both prone to recall bias**

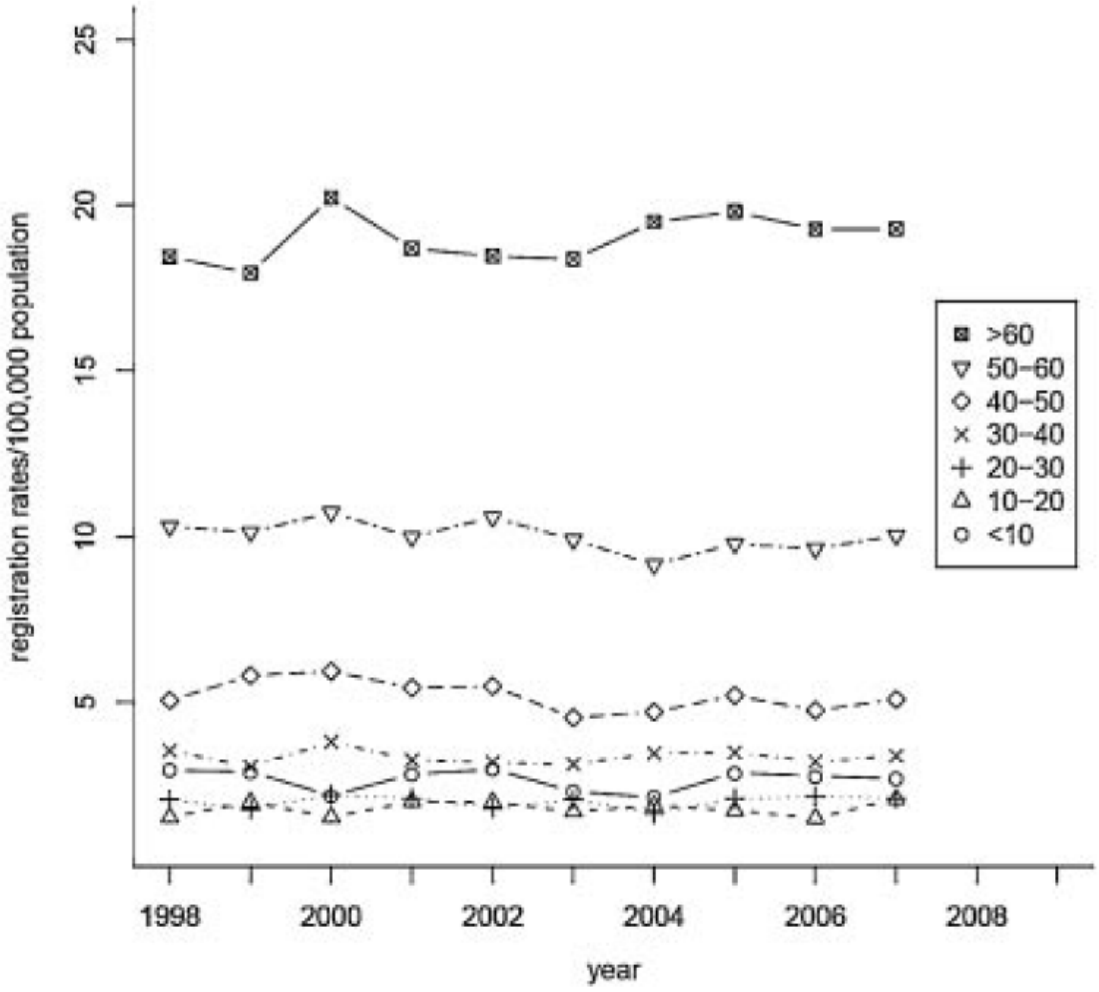
Incidence trends – glioma

- No increased incidence in age-groups where mobile phone use have been prevalent
  - → Studies available from Australia (including 2008), the Nordic countries (including 2008), the UK (including 2007), the US (including 2008), Sweden (including 2009)

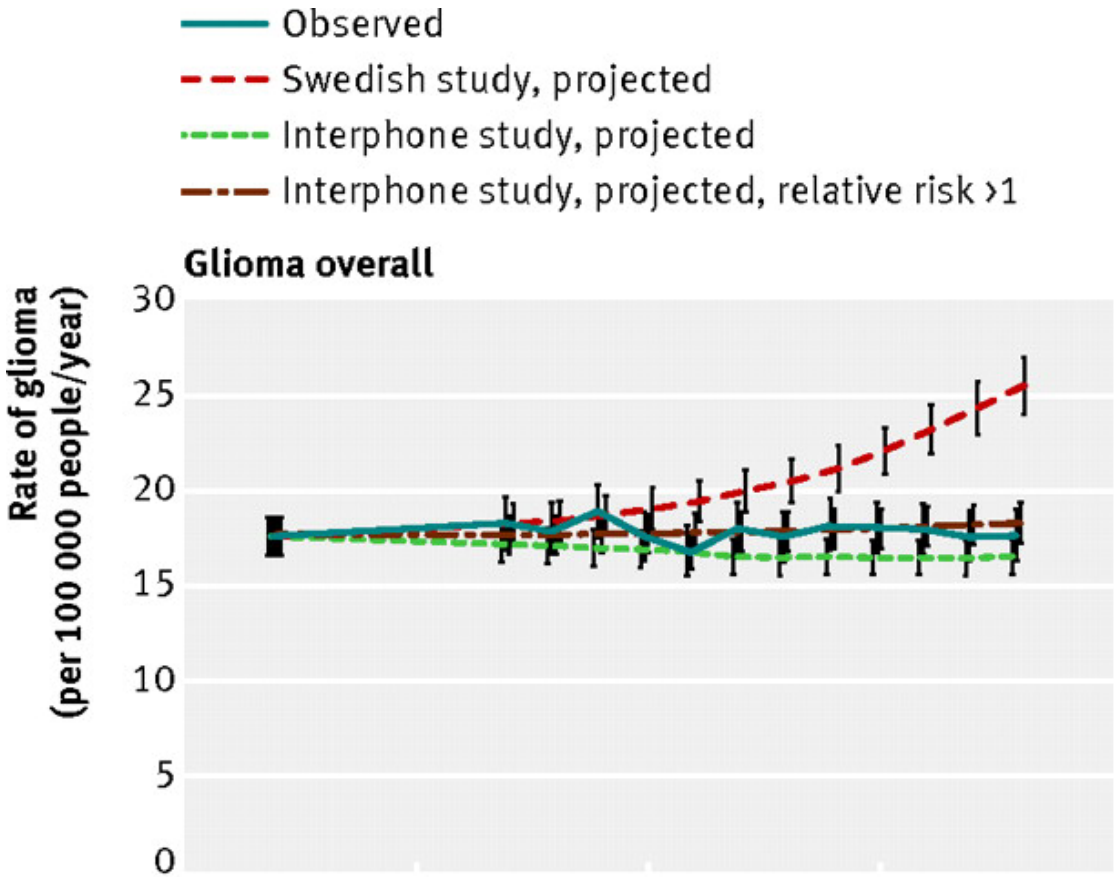
- Deltour et al., 2012, consistency check comparing the stable incidence trends with results from some case-control studies:
- **100% probability that**
  - → a RR of 2.0 with up to 15 years induction period
  - → a RR of 1.5 with up to 10 years induction period
  - → a RR of 1.2 with up to 5 years induction period
  - → 98% probability that a RR of 1.5 among heavy users (≥1640 h)

would be seen in incidence trends in the Nordic countries

UK: Age specific brain cancer incidence trends 1998-2007, de Vocht et al., Bioelectromagnetics, 2011



Observed and projected incidence of glioma in the US based on results from case-control studies



Little M P et al. BMJ 2012;344:bmj.e1147

Mobile phone use and childhood brain tumors

- So far only one study published (Aydin et al. JNCI 2011)
  - →Risk estimates slightly above unity, but non-significant
  - →No exposure-response relationship in terms of amount of mobile phone use or localization of the brain tumor

- Brain tumor incidence trends in children and adolescents remain stable since the introduction of mobile phones
  - →Published data from Australia, Nordic countries, Sweden, UK, US

Conclusions

- So far little evidence that mobile phone use affect brain tumor risk
- Incidence trends are not compatible with the few observed risk increases
- However, some uncertainties remain:
  - → Still short induction period – up to around 15 years
  - → Need to follow-up on the results for heaviest users
- Can only be done with prospective design combining self-reported and registered mobile phone use
  - → Must minimize recall bias and non-differential exposure misclassification, as well as selection bias
- Follow brain tumor incidence trends in high quality registers