The use of mobile phones and the risk of brain tumors among children and adolescents

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Dekan

A heavy snowfall disappears into the sea. What silence!

— FOLK ZEN SAYING

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Summary

Background

Mobile phones experienced a steep rise in popularity among children and adolescents during the last decade. The increase in popularity has been reflected in both increased ownership and increased usage of mobile phones. Most children start to use mobile phones when they are around 9–10 years old, but usage before school age is not uncommon. The increase in mobile phone use has raised concerns about possible adverse health effects. Brain tumors have been a main concern because the brain absorbs most of the radio frequency energy emitted by mobile phones during calls. In addition, it has been hypothesized that children may be more vulnerable to radio frequency electromagnetic fields (RF-EMFS) because their nervous system is developing, their brain tissue is more conductive than that of adults, and RF-EMFS penetrate in to regions that are deeper in their brains. Radio frequency radiation emitted by mobile phones has insufficient energy to directly damage the DNA and the only known effect of RF-EMFS is heating of the tissue. The lack of genotoxicity and carcinogenicity of mobile phone radiation has been confirmed by numerous experimental and animal studies. Studies about mobile phone use and brain tumor risk among adults have shown no increased risk for regular users but have been inconclusive regarding long-term (≥10 years) and heavy mobile phone use. The largest case-control study so far, the INTERPHONE study, found an increased risk for glioma among heavy users (≥1640 lifetime calls). Another study from a Swedish research group reported a five-fold increased risk for astrocytoma for adults who first used mobile phones before the age of

20. No study has addressed the association between mobile phone use and brain tumor risk among children and adolescents so far.

Objectives

The goal of this thesis was to assess whether there is a relationship between mobile phone use and brain tumor risk among children and adolescents or not. In addition, we also examined the impact of recall and selection bias in case-control studies about mobile phone use and brain tumors. Lastly, possible predictors of levels of mobile phone use as well as overestimation of recalled mobile phone use were assessed.

Methods

In 2006, we set up CEFALO, an international case-control study about the relationship between mobile phone use and brain tumor risk in children and adolescents aged 7–19 years. CEFALO was performed in Denmark, Sweden, Norway, and Switzerland. The study period ranged from 2004 through 2008. Children and adolescents of age 7–19 years who were diagnosed during the study period with a primary brain tumor were eligible. For each case patient, we selected two healthy control subjects matched by age, sex and geographical region of residence using population registries. Exposure data was collected by face to face interviews with the study participants accompanied by at least one parent. Risk estimates for brain tumors were calculated for various exposure surrogates. We also examined the gender and age-adjusted brain tumor incidence rates among Swedish children and adolescents aged 5–19 years from 1990 to 2008 including hypothetical incidence rate trends based on the risk estimates found in our analyses.

We conducted a simulation study to assess the impact of recall and selection bias on the result of case-control studies about mobile phone use and brain tumors. A random sample of 352 cases and 646 controls was drawn repeatedly from hypothetical case-control datasets that resembled central characteristics of the CEFALO population. Our

choice of levels of recall error was guided by a validation study that compared objective operator data with the self-reported amount of mobile phone use in CEFALO. To simulate selection bias, we varied the probabilities of users and non-users of mobile phones to be drawn from the case-control datasets. In addition, we studied plausible scenarios for CEFALO based on the results of the comparison between self-reported and operator-recorded mobile phone use. In these scenarios, we combined recall errors and selection bias. We considered various factors as possible predictors of amount of mobile phone use and of overestimation of recalled mobile phone use.

Results

Regular users of mobile phones were not statistically significantly more likely to have been diagnosed with brain tumors compared with non-regular users (OR=1.36, 95% CI=0.92 to 2.02). No clear exposure-response relationship was observed for any exposure surrogate. Moreover, no exposure-response relationship was seen in terms of localization of the tumor. For the study participants for whom operator-recorded data were available, we found a statistically significantly increased risk among users with more than 2.8 years since the start of the first subscription (OR=2.15, p_{trend}=0.001). The odds ratio for brain tumor risk among ipsilateral regular users of mobile phones was not higher than the odds ratio of contralateral regular users (OR=1.74 and OR=2.07). The risk estimate of 2.15 after 3 years of regular mobile phone use is incompatible with the stable (or even downward) incidence trends observed among Swedish children and adolescents aged 5–19 years from 1990 to 2008. This indicates that short-term use of mobile phones does not cause brain tumors in children and adolescents.

In the validation study, case patients overestimated their cumulative number of calls by 9% on average and controls by 34%. Case patients also overestimated their cumulative duration of calls by 52% on average and controls by 163%. We found little evidence for differential recall errors (p=0.20). Almost no bias in the odds ratio for regular use was observed in all plausible scenarios for CEFALO. However, we observed

downward biased ORs for heavy use in all scenarios when a true risk of mobile phones was assumed.

Participants of Sweden had statistically significantly less average number of calls per day (−61%) compared to participants from Denmark. Male participants tended to have a lower average number and duration of calls per day than female participants. Per year of age, average number and duration of calls per day increased by 7%, although not statistically significant. Older CEFALO participants (15–19 years) had a statistically significantly higher likelihood of overestimating their cumulative number and duration of calls compared to younger participants (7–14 years). Female participants were more likely to overestimate duration of calls than male participants. A higher amount of operator-recorded mobile phone use was associated with a lower probability of overestimating the mobile phone use.

Conclusions and Outlook

CEFALO is the first study to investigate the relationship between mobile phone use and brain tumor risk in children and adolescents. We found no consistent evidence for a causal association between short-term mobile phone use and brain tumor risk among children and adolescents. The lack of an exposure-response relationship either in terms of the amount of mobile phone use or by localization of the brain tumor argues against a causal relationship. These findings are corroborated by the fact that brain tumor incidence rates among children and adolescents have not increased in many countries in recent times. We cannot, however, exclude the possibility of a small increase in brain tumor risk due to mobile phone use. As we found that self-reported mobile phone use is affected with large random and some systematic recall errors, we emphasize the importance of future studies with objective exposure assessment or the use of prospectively collected exposure data. We also recommend the monitoring of time trends in brain tumor incidence rates as even a small risk should be reflected in future incidence rate trends.

We could also show that age and sex are related to the quality of recall of own mobile phone use. As a consequence, such factors act as confounders in studies relying only on self-reported mobile phone use and have to be considered in the analysis.

Zusammenfassung

Hintergrund

Die starke Zunahme des Handygebrauchs bei Kindern und Jugendlichen in den letzten 15 Jahren hat in der Bevölkerung zu Bedenken wegen möglicher Gesundheitsrisiken der hochfrequenten elektromagnetischen Felder (HF-EMF) geführt. Die meisten Kinder beginnen mit etwa 9–10 Jahren ein Mobiltelefon zu gebrauchen aber ein Handygebrauch im Vorschulalter ist nicht ungewöhnlich. Eine Erhöhung des Hirntumorrisikos war die Hauptbefürchtung, da beim Telefonieren mit einem Handy am Ohr das Hirn die meiste Strahlung absorbiert. Es wurde auch spekuliert, dass Kinder anfälliger für negative Effekte von hochfrequenten elektromagnetischen Strahlen sind da sich ihr Nervensystem noch in der Entwicklung befindet. Des Weiteren ist das Hirngewebe von Kindern leitfähiger als das von Erwachsenen und die Strahlung dringt tiefer ins Gehirn ein. Hochfrequente elektromagnetische Strahlung hat nicht genug Energie, um Moleküle oder die DNS direkt zu schädigen und der einzig bekannte Effekt von HF-EMF ist das Erwärmen des Gewebes. Die Absenz eines genotoxischen oder karzinogenen Effektes von HF-EMF wurde in zahlreichen Experimental- und Tierstudien bestätigt. Studien über den Zusammenhang zwischen Mobiltelefonen und Hirntumorrisiko bei Erwachsenen haben kein erhöhtes Risiko für regulären Handygebrauch gefunden. Es bestehen jedoch noch Unsicherheiten bei langfristigem (≥ 10 Jahre) und starkem Mobiltelefongebrauch. In der grössten Fall-Kontrollstudie bisher, der INTERPHONE-Studie, zeigte sich ein erhöhtes Risiko für Gliome für Personen, die mehr als 1640 Telefonate in ihrem Leben getätigt hatten. Eine Schwedische Studie berichtete ein fünffach erhöhtes Risiko für Astrozytome für Erwachsene, die vor dem

20. Lebensjahr mit dem Mobiltelefongebrauch begonnen hatten. Es gibt jedoch bislang keine Studie, die den Zusammenhang zwischen Mobiltelefongebrauch und Hirntumorrisiko bei Kindern und Jugendlichen untersucht hat.

Ziele

Das Ziel dieser Dissertation war es, den Zusammenhang zwischen Mobiltelefongebrauch und Hirntumorrisiko bei Kindern und Jugendlichen zu erforschen. Den Einfluss von Recall- und Selektionsbias auf die Resultate von Fall-Kontrollstudien über Mobiltelefongebrauch und Hirntumore sowie mögliche Prädiktoren der Häufigkeit des Mobiltelefongebrauchs und der Überschätzung bei selbst-berichtetem Mobiltelefongebrauch wurden ebenfalls untersucht.

Methoden

CEFALO ist eine internationale Fall-Kontrollstudie über den Zusammenhang zwischen Mobiltelefongebrauch und Hirntumorrisiko bei Kindern und Jugendlichen im Alter von 7–19 Jahren. Dänemark, Schweden, Norwegen und die Schweiz nahmen an CEFALO teil. Die Studienperiode war von 2004 bis 2008. Kinder und Jugendliche im Alter von 7–19 Jahren, die während der Studienperiode an einem primären Hirntumor erkrankten kamen als Studienteilnehmer in Frage. Für jeden Patienten wurden zwei gesunde Kontrollpersonen desselben Alters, Geschlechts und derselben geographischen Wohnregion aus Bevölkerungsregister ausgewählt. Expositionsdaten wurden mittels persönlichen Interviews mit den Studienteilnehmern und mindestens einem Elternteil erfasst. Risikoschätzer für Hirntumore wurden berechnet für diverse Expositionsmasse berechnet. Ebenfalls wurden die geschlechts- und altersadjustierten Trends der Hirntumorinzidenzraten von Schwedischen Kindern und Jugendlichen im Alter von 5–19 Jahren zwischen 1990 und 2008 mit hypothetischen Inzidenzraten, die auf den Risikoschätzern von CEFALO basierten, verglichen.

Eine Simulationsstudie wurde durchgeführt um die Auswirkungen von Recall- und Selektionsbias auf die Resultate von Fall-Kontrollstudien über Mobiltelefongebrauch und Hirntumore abzuschätzen. Eine zufällig ausgewählte Stichprobe von 352 Patienten und 646 Kontrollpersonen wurde wiederholt aus einem generierten hypothetischen Fall-Kontroll-Datensatz gezogen, welcher die zentralen Charakteristika des CEFALO-Kollektivs wiederspiegelte. Die Wahl der Ausmasse des Recall-Errors basierte auf einer Validationsstudie, in welcher objektive Daten von Mobilnetz-Betreiber mit dem selbst-berichteten Mobiltelefongebrauch in CEFALO verglichen wurden. Um Selektionsbias zu simulieren wurde die Wahrscheinlichkeit aus dem generierten Fall-Kontroll-Datensatz in die Studie aufgenommen zu werden variiert. Darüber hinaus wurden plausible Szenarien für CEFALO gerechnet, die auf der Validationsstudie basierten und sowohl Recall- als auch Selektionsbias enthielten. Wir berücksichtigten mehrere Faktoren als mögliche Prädiktoren der Häufigkeit des Mobiltelefongebrauchs und der Überschätzung des selbst-berichteten Handygebrauchs.

Resultate

Reguläre Mobiltelefonbenutzer hatten keine statisch signifikant erhöhte Wahrscheinlichkeit, mit einem Hirntumor diagnostiziert zu werden verglichen mit nicht-regulären Handybenutzern (OR=1.36, 95% KI=0.92 bis 2.02). Es wurde für keines der Expositionsmasse eine klare Expositions-Wirkungs-Beziehung beobachtet. Insbesondere wurde keine Expositions-Wirkungs-Beziehung beobachtet was die Lokalisation der Tumore betrifft. Wir fanden für diejenigen Studienteilnehmer mit Daten der Netzwerkbetreiber ein statistisch signifikant erhöhtes Risiko für Nutzer, denen erstes Abonnement mehr 2.8 Jahre zurücklag (OR=2.15, 95% KI=1.07 bis 4.29, p_{Trend}=0.001). Die Odds Ratio für ipsilateralen regulären Mobiltelefongebrauch war nicht höher als die Odds Ratio für kontralateralen Gebrauch (OR=1.74 und OR=2.07). Eine Erhöhung des Hirntumorrisikos um den Faktor 2.15 nach 3 Jahren regulären Gebrauchs ist inkompatibel mit den beobachteten stabilen Trends der Hirntumorinzidenzraten von Schwedischen Kindern und Jugendlichen im Altern von 5–19 Jahren zwischen 1990

und 2008. Das weist darauf hin, dass kurzfristiger Mobiltelefongebrauch keine Hirntumoren bei Kindern und Jugendlichen verursacht.

In der Validierungsstudie haben Patienten ihre kumulative Anzahl Anrufe im Schnitt um 9 % und die Kontrollen um 34 % überschätzt. Die Patienten überschätzten auch die kumulative Dauer der Anrufe um 52 % und die Kontrollen um 163 %. Es wurde keinen Hinweis darauf gefunden, dass sich Patienten und Kontrollpersonen hinsichtlich der Recall-Error unterscheiden (p=0.20). Fast keine Schätzfehler der Odds Ratio für regulären Mobiltelefongebrauch wurde beobachtet in allen plausiblem Szenarien für CEFALO. Jedoch unterschätzte die simulierte Odds Ratio für starken Mobiltelefongebrauch das wahre Risiko, sobald ein Zusammenhang zwischen Mobiltelefongebrauch und Hirntumoren angenommen wurde.

Studienteilnehmer aus Schweden hatten im Schnitt signifikant weniger Anrufe pro Tag (−61 %) verglichen mit Studienteilnehmer aus Dänemark. Männliche Studienteilnehmer zeigten die Tendenz zu weniger und kürzeren Anrufen pro Tag verglichen mit weiblichen Studienteilnehmern. Pro Lebensjahr stieg die Anzahl und Dauer der Anrufe pro Tag um 7 %, wenn auch nicht statistisch signifikant. Ältere CEFALO Studienteilnehmer (15–19 Jahre) hatten eine signifikant höhere Wahrscheinlichkeit ihre Anzahl und Dauer der Anrufe zu überschätzen verglichen mit 7–14-Jährigen. Weibliche Studienteilnehmer hatten eine höhere Wahrscheinlichkeit, ihre Anzahl und Dauer der Anrufe zu überschätzen verglichen mit männlichen Teilnehmern. Je höher der von den Netzbetreibern aufgezeichnete Mobiltelefongebrauch war, desto kleiner war Wahrscheinlichkeit den Mobiltelefongebrauch zu überschätzen.

Schlussfolgerungen und Ausblick

CEFALO ist die erste Studie die den Zusammenhang zwischen Mobiltelefongebrauch und Hirntumoren in Kindern und Jugendlichen untersuchte. Es wurde keine konsistenten Hinweise auf einen kausalen Zusammenhang zwischen kurzfristigen Mobiltelefongebraucht und dem Hirntumorrisiko unter Kindern und Jugendlichen gefunden.

Das Fehlen einer Expositions-Wirkungs-Beziehung was die Häufigkeit des Mobiltelefongebrauchs einerseits und die Lokalisierung der Hirntumore andererseits betrifft spricht gegen einen Kausalzusammenhang. Diese Resultate werden von der Tatsache gestützt, dass die Inzidenzraten von Hirntumoren bei Kindern und Jugendlichen in vielen Ländern in den letzten Jahren nicht anstiegen. Ein geringfügig erhöhtes Hirntumorrisiko aufgrund von Mobiltelefongebrauch kann allerdings nicht gänzlich ausgeschlossen werden. Weil der selbst-berichtete Mobiltelefongebrauch mit grossen zufälligen und in geringerem Masse auch mit systematischen Fehlern behaftet ist, ist eine objektive Expositionserfassung oder die Nutzung von prospektiv erfassten Expositionsdaten in zukünftigen Studien von grosser Wichtigkeit. Ebenfalls wird die Überwachung der Trends von Hirntumorinzidenzraten empfohlen, da schon geringfügig erhöhte Risiken eine Erhöhung der Inzidenz zur Folge hätten.

Es wurde gezeigt, dass das Alter und das Geschlecht mit der Qualität des selbstberichteten Mobiltelefongebrauches in Verbindung stehen. Als Konsequenz agieren solche Faktoren als Störvariablen (Confounder) in Studien, die ausschliesslich selbstberichteten Mobiltelefongebrauch als Expositionsmass verwenden und müssen in der Analyse berücksichtigt werden.

List of abbreviations and definitions

Abbreviations

CI	Confidence interval
COSMOS	Cohort study of mobile phone use and health
DECT	Digital enhanced cordless telecommunications
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
EHS	Electromagnetic hypersensitivity
ELF	Extremely low frequency
EMF	Electromagnetic field
GSM	Global system for mobile communication
HERMES	Health effects related to mobile phone use in adolescents
HMP	Hardware modified phone
HZ	Hertz (1/s)
ICNIRP	International Commission on Non-Ionizing Radiation Protection

IEI-EMF	Idiopathic environmental illness with attribution to electromagnetic fields
IQR	Interquartile range
IRR	Incidence rate ratio
LTE	Long Term Evolution
OR	Odds ratio
PNET	Primitive neuroectodermal tumor
PY	Person-years
QUALIFEX	Health-related quality of life and radio frequency electromagnetic field exposure: prospective cohort study
RF-EMF	Radio frequency electromagnetic field
RR	Relative risk
SAR	Specific energy absorption rate (W/kg)
SES	Socioeconomic status
SMP	Software modified phone
UMTS	Universal mobile telecommunications system

Definitions

Nocebo effect	Inverse of the placebo effect, meaning that adverse health symptoms occur due to expectations (e.g. due to health concerns)

1 Introduction and background

1.1 The electromagnetic spectrum

Electromagnetic radiation is characterized by its wavelength and frequency. The frequency is expressed in Hertz (HZ) which is defined as number of oscillations per second. Electromagnetic waves with a higher frequency are more energetic than waves with a lower frequency. Specifically, the energy of the electromagnetic wave is proportional to its frequency. Some electromagnetic radiation contains enough energy to remove electrons from atoms or molecules leaving behind positively charged ions or molecules which may subsequently damage other molecules such as the DNA or break molecular bonds.[1] Electromagnetic radiation containing enough energy to ionize atoms or molecules is called ionizing radiation while radiation with insufficient energy to ionize atoms or molecules is called non-ionizing radiation. Examples of ionizing radiation are X-rays and gamma rays while visible light, infrared and radiation from mobile phones are non-ionizing. Non-ionizing electromagnetic fields can further be divided into static fields (0 HZ), extremely low frequency (ELF) magnetic and electric fields (up to 100 KHZ) and radiofrequency electromagnetic fields (RF-EMFS, 100 KHZ–300 GHZ) with mobile phone radiation belonging to the latter.[2] ELF magnetic and electric fields are produced when electricity is transmitted in power lines and cables or used in electrical devices such as hairdryers. ELF magnetic and electric fields can induce electrical fields and currents inside the body. The absorption of radiofrequency electromagnetic fields (RF-EMFS) can lead to heating and local damage of biological tissues.[3]

1.2 Characteristics of mobile and cordless phone radiation

The radiation emitted by mobile phone handsets heavily depends on the network technology/generation. GSM 900 mobile phone handsets (second generation, 2G) emit radiation in the frequency range of 880–915 MHZ and a wavelength of 33–34 cm. GSM 1800 mobile phone handsets emit radiation in the frequency range of 1710–1785 MHZ and a wavelength of 17–18 cm. UMTS mobile phones handsets (third generation, 3G) emit radiation in the frequency range of 1920–1980 MHZ and a wavelength of 15–16 cm.

Mobile phone handsets frequently communicate with mobile phone base stations (fixed transmitters) either to register themselves, to transmit data (e.g. a text message or internet traffic) or during calls. Data transfer from the mobile handset to the base station is called uplink whereas data transfer from the base station to the mobile handset is called downlink. Mobile phone handsets can also emit radiation when they are just switched on but not in use. This is due to location updates. A location update occurs when the mobile phone handset is moving from one radio cell (i.e. area covered by a base station) to another.[4] During this procedure, the mobile device informs the network whenever it moves from one radio cell to another. When the mobile phone is used for a call and is moving from one cell to another, a handover occurs. During a handover the data stream is handed over from one base station to the other.

Cordless phones (DECT: Digital enhanced cordless telecommunications) emit radiation with a frequency of 1880–1900 MHZ and a wavelength of 16 cm.

A feature used by second generation GSM networks aimed at reducing the output power of mobile phones is adaptive power control (APC). Adaptive power control starts with the maximum output power of the mobile phone handset and reduces the power over time to the lowest level compatible with a good signal quality.[5] A recent study has shown, however, that this technology is not very effective in reducing the output power and that the average power output was approximately 50% of the maximum.[6]

Third generation UMTS networks use an improved power control technology and the average output power is usually only 1% of the maximum (compared to 20–50% among GSM phones).[7] Thus, the average output power of UMTS phones is 100–500 times lower than that of typical GSM phones during average use.[7,8]

The fourth network generation (4G) is called Long Term Evolution (LTE). Starting from 2010, Long Term Evolution networks have been continuously brought into service in Switzerland. In addition to all frequency bands of the GSM and UMTS networks, LTE will also use the frequency bands of 800 MHZ and 2.6 GHZ.[9] There are at least 15 LTE networks operational in 11 different countries as of 2011. Because of the rapid increase of mobile data traffic this number is likely to increase in the future.

1.3 Health effects of mobile phone radiation: state of research and open issues

Mobile phones experienced a steep increase in popularity and ownership both among adults, children, and adolescents in the last 20 years (Figure 1-1).[10-13] As of 2010 it is estimated that there are more than 5 billion mobile phone subscribers worldwide (Figure 1-2). In many countries, the penetration rate (i.e. the number of mobile phone subscription divided by the population) already exceeded 100%. The rapid increase in mobile phone use has raised concerns in the general public about possible adverse health effects of such devices. Because mobile phones are held in proximity to the head during calls, tumors of the head and neck were of primary concern. It has been proposed that children may be more vulnerable to RF-EMFS for several reasons: I) they have a lifetime exposure, II) they experience greater absorption of RF energy in the tissues of the head at mobile telephone frequencies because they have a smaller head circumference, and III) their scalp is thinner than that of adults and they have a still developing nervous system.[14] Recent modeling studies indicated that energy absorption in heads of younger children at around the age of 8–10 years may indeed be increased.[15,16] Furthermore, some tissues like the bone marrow are more conductive among children that among adults and experience a greater exposure.[16] A recent sys-

tematic review of cellular and animal studies, however, concluded that there is little support for the claim that the young are more sensitive than adults.[17] Furthermore, a provocation study that exposed boys aged 14–15 years to GSM 900 phone radiation for 15 minutes found no evidence for adverse thermal effects such as a change in local cerebral blood flow, an increase of ear canal temperature or a change of autonomic nervous system function.[18]

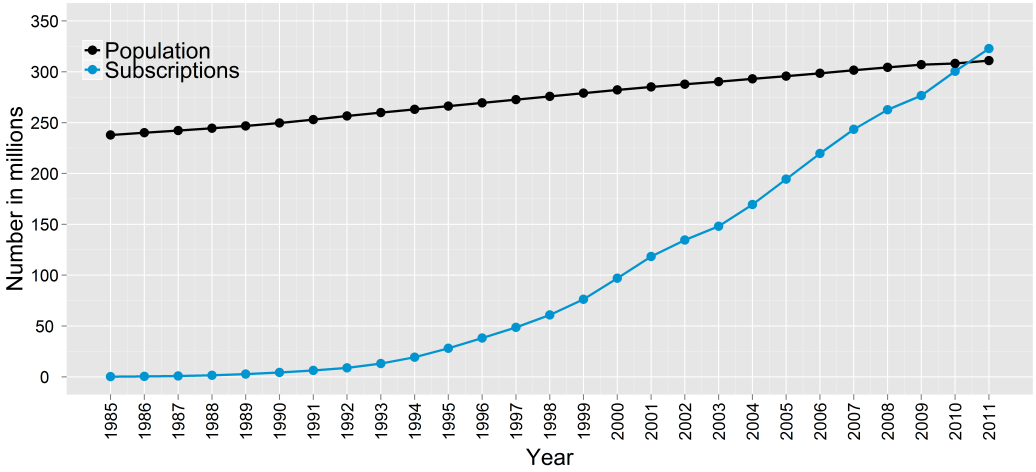

Figure 1-1 Number of wireless subscribers and total population in the United States between 1985 and June 2011. Source: CTIA (Cellular Telephone Industry Association, www.ctia.org, accessed 7. December 2011) and US Census Bureau (www.census.gov/population/international/data/, accessed 26. March 2012).

Numerous studies have addressed the proposed relationship between mobile phone use and brain tumor risk among adults. Because brain tumor incidence is low, most studies used the case-control approach.[19] In case-control studies, a group of individuals with the disease of interest (cases) are identified and their exposure status is assessed. For comparison, a group of people without the disease (controls) is randomly selected from the source population that gave rise to the cases. The potential relationship between the disease and the exposure(s) is then examined by comparing the cases and controls with respect to their exposure.[20] Case-control studies are usually less

expensive and easier to conduct than cohort studies, especially for rare diseases. In a case-control study, only one disease but many exposures can be studied. Because the exposure is assessed after the onset of the disease, case-control studies are therefore sometimes called *retrospective* studies. Recall bias, referring to inaccurately recalled exposure data, are often a serious problem in case-control studies, because information about the exposure is frequently assessed by questionnaires, relying solely on the participant's ability to recall past exposures (see section 1.4.3.4 on page 43 for a detailed explanation). Selection bias may also occur if participation in the study is associated with the exposure and the outcome (e.g. mobile phone owners may be more likely to participate in a study about mobile phone use and brain tumors than non-owners). Selection bias is explained in detail in section 1.4.3.3 on page 42.

The largest case-control study among adults so far is the INTERPHONE study. The INTERPHONE study is an interview-based case-control study that included 16 study centers and 13 countries with a total of 2708 glioma and 2409 meningioma cases.[21,22] In the pooled analysis of all national INTERPHONE data, the researchers found decreased risks for glioma (OR=0.81, 95% CI=0.70 to 0.94) and meningioma (OR=0.79, 95% CI=0.68 to 0.91) for regular use of mobile phones which was defined as an average of at least one call per week for a period of 6 months or longer. A statistically significantly elevated odds ratio was observed, however, for the 10th decile of recalled cumulative call time (≥1640 hours) for glioma (OR=1.40, 95% CI=1.03 to 1.89) but not for meningioma (OR=1.15, 95% CI=0.81 to 1.62). The authors concluded that the observed increased risk for glioma is most likely attributable to recall error and selection bias. Recently, a simulation study showed that the statistically significantly decreased odds ratio for glioma among regular users (OR=0.81) and the increased risk for glioma for heavy users (OR=1.40) are virtually incompatible with the observed incidence rate time trends in the Nordic countries (i.e. Denmark, Finland, Norway, and Sweden) and therefore, were most likely caused by biases and errors.[23] The INTERPHONE study was criticized for apparent methodological flaws such as inaccurate exposure assessment, low participation rates, and small numbers of long-term (≥10 years) and heavy users of mobile phones.[24,25]

While most studies about brain tumor risk and mobile and cordless phone use found no evidence for an increased brain tumor risk, some studies have found increased risks for brain tumors among long-term users of mobile telephones.[26-28] The numbers of brain tumor case patients with long-term use of mobile phones, however, are still too low to draw definite conclusions from these studies.[29] In addition, a study group from Sweden has consistently reported increased brain tumor risk among mobile and cordless phone users.[30-42] One study reported odds ratios for astrocytoma as high as 4.4 (95% CI=1.9 to 10) and 5.2 (95% CI=2.2 to 12) for cordless and mobile phone use before the age of 20, respectively.[30] These studies were criticized, however, for several methodological shortcomings which may explain the deviation of the findings from those of other investigators.[26] Furthermore, the high risk estimates reported by Hardell and colleagues are thought to be incompatible with recent nationwide studies that investigated brain tumor incidence rate trends and consistently found no evidence for increasing brain tumor incidence rates.[23,43-53] There is, however, one study that found increasing incidence rates for glioblastoma multiforme and meningioma in Australia, particularly after 2006.[54]

Studies about mobile phone use and acoustic neuroma (vestibular schwannoma, i.e. a benign tumor of the eighth cranial nerve) risk yielded similar results as the studies about glioma and meningioma.[32,55-59] The INTERPHONE study which comprises the largest number of long-term users of mobile phones (>10 years) up to date found no increase in risk of acoustic neuroma with ever regular use of mobile phones or for users who began regular use 10 years or more before the diagnosis date.[56] As for glioma, the researchers found an elevated risk for the highest level of cumulative duration of calls (≥1640 hours). This finding could be due to chance, recall bias or a causal effect. Acoustic neuroma is a slowly growing tumor and studies that investigate long-term users of mobile phones are warranted.

Most studies that investigated the relationship between mobile phone use and brain tumor risk have used the case-control design. There is, however, a large Danish subscriber cohort study including all Danes aged 18 or more that were born in Denmark

after 1925.[60-62] The most recently published update included 358'403 subscription holders with a total of 3.8 million person-years.[60] Strikingly, the study found no evidence for an increased risk for brain tumors among the long-term users (≥13 years) of mobile phones (incidence rate ratio [IRR]=1.03, 95% CI=0.83 to 1.27 for men and IRR=0.91, 95% CI=0.41 to 2.04 for women). Furthermore, no indication of an exposure-response relationship either by years since first subscription or by anatomical location of the tumor was observed.

Since mobile phones were not regularly used until the 1990s, currently published studies have had little power to detect possible cancerogenic effects involving long induction periods or long-term heavy exposure to mobile phones.[23] Moreover, there is currently no established biological mechanism for carcinogenicity of low-dose microwave radiation from mobile phones.[19,63] The generally accepted consensus is that the heating of the tissue by mobile phone radiation is negligible and that any possible carcinogenic effect would have to be mediated through a non-thermal mechanism such as an impairment of the DNA repair mechanisms. Other proposed carcinogenic mechanisms are: increased intracellular radical formation via the Fenton reaction,[64,65] movement of electrons with temporary formation of guanine radicals that can lead to oxidative damage,[66-69] and influence on the structure and function of proteins related to DNA metabolism.[70-77]

Claims of carcinogenicity of RF-EMFs have also been investigated *in vitro* and *in vivo* by a large number of studies, including studies in mice and rats. Recent reviews of these studies concluded that although some studies found evidence for carcinogenic effects of RF-EMF, the majority of the studies reported negative results.[78-81] The researchers stated that the current evidence does not support the assumptions that exposure to such fields is carcinogenic for humans. One systematic review investigated the important question whether the young are more sensitive to the effects of RF-EMFs than adults.[17] The researchers came to the conclusion that the available evidence from cellular and animal studies does not suggest that the young are more sensitive to RF-EMFs than adults. Interestingly, RF-EMFs with the characteristics of a typ-

ical UMTS signal on failed to elicit any effect on several key cellular endpoints in a recent study, despite the very high SAR of 10 W/kg.[82] Results from experimental studies with cell cultures or animal models, however, do not necessarily apply to humans. On the other hand, some studies even provide promising evidence that electromagnetic fields inhibit cancer cell proliferation and are effective in treating liver cancer.[83-85] Interestingly, some studies have found that electric fields stop cell proliferation in human brain tumors and metastatic spread of lung tumors.[86,87] The frequencies of the fields used in these studies are different from the frequencies of mobile phones, however.

In short, many non-thermal mechanisms of carcinogenesis of RF-EMFS have been proposed but despite considerable effort to elucidate them, heating of tissue remains the only adverse health effect of RF-EMFS to date.[81,88] Consequently, current guidelines released by the ICNIRP (International Commission on Non-Ionizing Radiation Protection) for limiting exposure to RF-EMFS aim at preventing adverse health effects due to heating of the tissue.[3]

Besides brain tumors, other public health concerns included unspecific symptoms of ill health particularly headaches, fatigue, perceived stress, and impairments of sleep quality.[89-100] It is estimated that about 1.5 to 10% of people across Europe and the USA claim to be affected by electromagnetic fields.[96,101,102] This phenomenon is described as electromagnetic hypersensitivity (EHS) or idiopathic environmental illness with attribution to electromagnetic fields (IEI-EMF).[92,103-107] Recently, a meta-analysis that studied the acute effects of electromagnetic fields emitted by GSM mobile phones on subjective well-being and physiological reactions found no significant impact of short-term RF-EMF exposure on any parameter.[100]

The QUALIFEX study (health-related quality of life and radio frequency electromagnetic field exposure: prospective cohort study) combined objectively collected personal RF-EMF measurements with RF propagation modeling to develop for RF-EMF exposure assessment for a large population.[108-112] In the main study, QUALIFEX com-

bined the exposure prediction model to predict individual exposure to RF-EMFs with a questionnaire survey to investigate the impact of RF-EMF exposure in daily life on health-related quality of life and sleep.[113] The main study enrolled 1375 participants and the follow-up time was one year. The researchers found little evidence for a connection between RF-EMF exposure and non-specific health symptoms or tinnitus. Also, no relationship between self-reported and objectively measured sleep quality and RF-EMF exposure was found.[114,115]

Research regarding the short-term effects of electromagnetic fields like those from mobile phones on the sleep electroencephalogram (EEG) yielded inconsistent results. Some studies consistently reported alterations in the spindle frequency (8–14 Hz) of the EEG during sleep.[116-122] Usually, no alteration in subjective sleep quality after exposure to RF-EMFs was observed.[116,121,122] The possible impact of the observed alterations of sleep EEG on sleep quality or quality of life is unclear so far. Other agents, such as caffeine are also well-known to alter sleep EEG.[123] Other studies, on the other hand, failed to show an effect of RF-EMFs exposure on various sleep outcomes.[124-128] A recent study, however, suggested that the effect of RF-EMFs on the subsequent EEG during sleep is sensitive to individual variability.[121] On the basis of their results, the authors concluded that previous negative research on the EEG during sleep is not strong evidence for a lack of effects of mobile phones. In a recent prospective cohort study investigating the long-term effects of objectively measured RF-EMFs on sleep quality, Mohler et al.[115] found no evidence for adverse effects on sleep quality from everyday RF-EMF exposure. On the other hand, a recent prospective cohort study found evidence for a relation between high frequency of mobile phone use and mental health outcomes among young adults.[98] Another explorative prospective study found evidence for a link between the use of different types of information and communication technology (i.e. mobile phones, computer, e-mailing, chatting etc.) and perceived stress, symptoms of depression and sleep disturbances among young adults.[97] Moreover, in a recent cross-sectional survey, significantly more sleep disturbances were found among Japanese adolescents that used mobile phones after lights out compared to adolescentes that did not use mobile phones after lights out.[99]

Laboratory based provocation studies have been performed to investigate the effects of electromagnetic fields on the development of non-specific health symptoms. Systematic reviews of such provocation studies, however, conveyed no evidence that electromagnetic hypersensitivity is causally related to the presence of electromagnetic fields.[92,104,129] It is probable that the concerns of negative health effects of RF-EMFs itself could lead to health impairments. This well-known effect is called *nocebo effect* and has been observed in several studies.[92,100,104,130-134] There is one study that claimed having found direct evidence for non-psychological EMF hypersensitivity.[135] The study, however, was only based on one subject.

In conclusion, the majority of recent systematic reviews that summarized the available evidence for a relationship between mobile phone use and brain tumors do not support a causal relationship between mobile phones and cancers of the head among adults.[26,81,136] The evidence for mobile phone use longer than 10 years and for heavy use of mobile phones is less clear and some reviews reported statistically significantly increased risks for long-term use of mobile phones.[137-141] The fact that a possible causal link between RF-EMFs and cancer risk cannot be completely ruled out has led the International Agency for Research on Cancer (IARC) to classify RF-EMFs as "possibly carcinogenic to humans" (Group 2B).[142] This means that there is limited evidence from human studies and less than sufficient evidence from experimental animal studies. In addition, a review by Huss and colleagues[143] found that experimental studies about health effects of mobile phone use funded exclusively by the industry were substantially less likely to report statistically significant effects on several end points possibly relevant to health (odds ratio for reporting at least one statistically significant result=0.11, 95% CI=0.02 to 0.78 compared to studies funded by public agencies or charities).

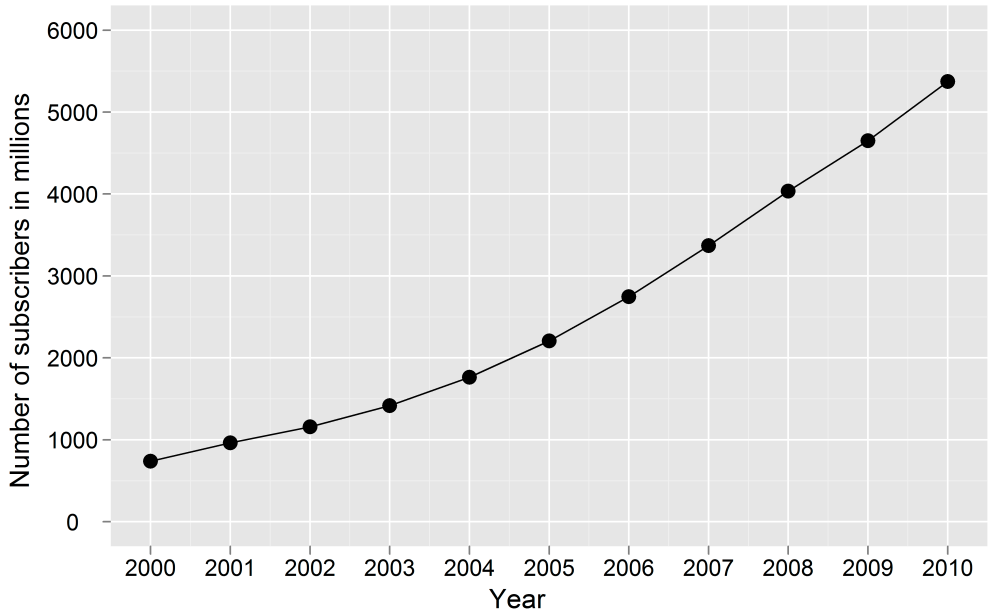

Figure 1-2 Number of mobile phone subscriptions worldwide. Source: ITU World Telecommunication/ICT Indicators database (www.itu.int/ITU-D/ict/statistics/, accessed: 8. November 2011).

1.4 Environmental cancer epidemiology

Epidemiology studies the distribution and determinants of health-related states or events in specific populations, and the application of this study to control of health problems.[20] Cancer epidemiology is a special case of epidemiology concerned with cancer.[144]

Environmental epidemiology is a subspecialty of epidemiology that studies the health effects on a specific population of exposure to physical, chemical, and biological agents that are external to the human body.[20] It also includes social, economic, and cultural factors that are related to these physical, chemical, and biological agents. Thus, the term *environment* generally refers to all non-genetic factors.[145]

Finally, environmental cancer epidemiology refers to the study of environmental factors affecting the occurrence of cancer. Primary outcomes include cancer incidence, prevalence, survival, and mortality.[20]

1.4.1 Important concepts in cancer epidemiology

1.4.1.1 Prevalence

Prevalence is a measure of disease status.[20] It is defined as total number of individuals who have a disease at a particular time (or time period) divided by the population at risk of contracting the disease at that time.

1.4.1.2 Incidence

The incidence rate is the rate at which new events (e.g. diseases) occur in a population.[20] It is defined as the total number of individuals in a specified population that develop a disease in a particular time period divided by the total number of individuals at risk of developing the disease during that time period (the denominator is usually called *person-time* and is usually 100'000 person-years [PY]). An incidence rate of 13 per 100'000 person-years means that for every 100'000 person-years experienced (that could be 100'000 persons for one year or 200'000 persons for half a year and so on) 13 new cases of the disease occurred.

1.4.2 Association versus causation

One of the most important goals of epidemiology is the establishing of a causal relationship between a certain exposure and a certain disease.[146] The knowledge of a causal factor of a disease is vital in prevention of the disease by eliminating or reducing the exposure to the factor causing the disease. Often, a statistical association or correlation between a factor and a disease is observed. The observed association may

be causal or non-causal. An association is called causal if it is unlikely to be explained by external differences between the study groups or between exposed and non-exposed. There are, however, several reasons that lead to a spurious association between a factor and the diseases under study such as confounding or bias. Guidelines first published by the English epidemiologist Sir Austin Bradford Hill exist for judging whether an association is causal or not.[147,148] Although the so called Hill criteria are widely accepted among epidemiologists, most scientists refuse to use a simple checklist for the interpretation of study results.[145] Also, less consensus exists among epidemiologists about the practical application of the Hill criteria.

Formally, let Y be an outcome variable (e.g. cancer), and A being a treatment variable. Further, let $Y^{a=1}$ (read outcome Y under treatment a=1) be the outcome that would have been observed under the treatment value a=1, and $Y^{a=0}$ (read outcome Y under treatment a=0) the outcome variable that would have been observed under the treatment value a=0.[149] Association exists if $\Pr[Y=1 \mid A=1] \neq \Pr[Y=1 \mid \boldsymbol{A}=0]$, where Pr denotes probability. Causation exists if $\Pr[Y^{a=1}=1] \neq \Pr[Y^{a=0}=1]$ or $\mathrm{E}[Y^{a=1}] \neq \mathrm{E}[Y^{a=0}]$, where E denotes the expected value (Figure 1-3).

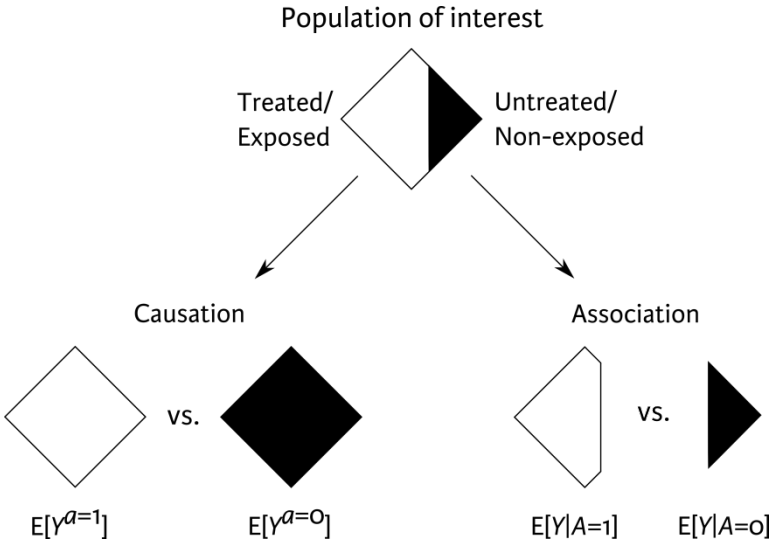

Figure 1-3 Difference between causation and association. The definition of causation implies a contrast between the whole white and the whole black diamond, whereas association implies a contrast between the white and the black areas of the original diamond. In the last line, the letter E denotes the expected value (adapted from Hernán and Robins[149]).

Association is defined by a different risk in two disjoint subsets of the population determined by the subjects' actual treatment value (A=1 or A=0). Causation, on the other hand, is defined by a different risk in the entire population under two different treatment values (a=1 or a=0). Usually, one cannot study all counterfactual outcomes in the entire population under all treatments/exposures. Therefore, associations from real world data must be used for causal inference under given conditions.[149]

1.4.3 Random errors and biases

It is very seldom that an epidemiological study comprises the whole population. Usually, only a subsample of the population is studied. The subsample is often a random selection of the reference population which ensures that the subsample resembles the reference population in some way.[150] There are, however, always random differences

in some respect between the subsample and the source population. These random errors are neither systematic nor differential and are the higher the smaller the subsample is.

Bias, on the other hand, is any systematic error of results resulting from methodological flaws in the study design, conduct or analysis.[20,146] In the framework of directed acyclic graphs (DAGs), bias is any structural association between exposure/treatment and outcome that does not arise from the causal effect of exposure/treatment on outcome.[149] Bias can be classified into three groups: I) confounding (common causes), II) selection bias (conditioning on common effect), and III) information bias (cause and effect).[151]

1.4.3.1 Confounding

Confounding is an important issue in almost all epidemiological study designs. The standard definition of a confounder includes three conditions: I) it must be associated with the disease (but must not be an effect of the disease) II) it must be associated with the exposure and III) it must not be an effect of the exposure.[145] Within the framework of causal inference, only the concept of confound*ing* exists without a clear definition of confoun*der*.[149] In the language of directed acyclic graphs (DAGs), confounding is present if exposure and outcome share a *common cause* (i.e. a backdoor path exists; Figure 1-4).[149] Any variable that can be used to block a backdoor path (by conditioning on it) can be viewed as a confounder (Figure 1-5).

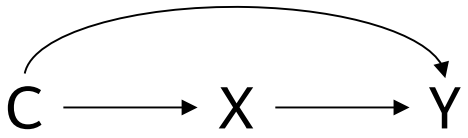

Figure 1-4 Directed acyclic graph (DAG) of an exposure (X) and an outcome (Y) with a common cause (C). In this case, confounding is present because a backdoor from X

over C to Y is open. By conditioning on C (i.e. adjusting for C), the backdoor path is closed and no confounding is present anymore.

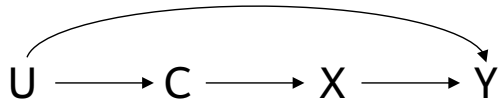

Figure 1-5 Directed acyclic graph (DAG) of an exposure (X), an outcome (Y), a measured covariate (C) and an unmeasured covariate (U). Even though C is not a common cause of X and Y, it can be viewed as a confounder since conditioning on C (i.e. adjusting for C) blocks the backdoor path from X over C and U to Y. After adjusting for C, no confounding is present anymore.

A prominent example of a confounder is smoking in a study that investigates the relationship between alcohol consumption and lung cancer. It is known that smokers have higher alcohol consumption and that smoking is a strong risk factor for lung cancer. Hence, smoking acts as a confounder because it is related to the exposure (alcohol consumption) as well as to the outcome (lung cancer) but is itself not an effect of the exposure. If the researchers do not control for smoking status in their analyses, a spurious association between alcohol consumption and lung cancer will be observed.[144]

Several approaches are available to handle the problem of confounding in case-control studies. On the level of the design and conducting of the study, the possibility of *matching* exists.[144,146,152] If a factor is suspected to be a confounder, we can match the cases and the controls for that factor (i.e. age, gender, geographical region). This means that no differences exist between cases and controls with respect to the distribution of the matched factor and the factor can therefore no longer act as confounder in the study. On the level of data analysis, we can *stratify* or *adjust* for confounders. Stratification simply means that the association is estimated separately for different strata of the factor that is suspected to be a confounder. Adjustment is commonly used in regression analysis and means that the factor that is suspected to be a con-

founder is included in the model. In multiple regression analysis, the effects of the variables are adjusted for all other variables included in the model. Therefore, the inclusion of a suspected confounder in the model is expected to change the association between the exposure of interest and the disease. By including the confounder in the model, the effect of interest is then adjusted for the confounder. There are, however, situations where the standard definition of a confounder is wrong and adjusting for the confounder actually introduces a bias (Figure 1-6).[149]

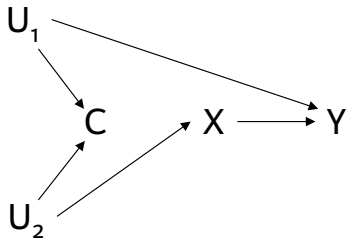

Figure 1-6 Directed acyclic graph (DAG) of an exposure (X), an outcome (Y), a measured covariate (C) and two unmeasured covariates (U_1 and U_2). C is both associated with the exposure X and the outcome Y and is itself not in the causal pathway of the disease (between X and Y). C is therefore a confounder by the standard definition. C is also a *collider* because two arrows end at C. A collider stops the flow of association and therefore, no backdoor path from X to Y is open and no confounding is present. By adjusting for C, the backdoor path is opened (conditioning on a collider opens the flow of association) and a bias is introduced.

1.4.3.2 Effect modification

Effect modification exists if an effect measure of a factor under study varies between levels of another factor.[20] If, for example, an effect estimate differs between age groups or between men and women, then age or sex are called effect modifiers. Practically, an effect modification is detected by including an interaction in the statistical model.[152] No adjustment exists for effect modification. A factor can be both a con-

founder and an effect modifier (e.g. asbestos in a study about smoking and lung cancer).

1.4.3.3 Selection bias

The participation in an epidemiological study is usually voluntary. In every study, there will be individuals that would be eligible to participate in the study but who do not want to participate. If the non-participants differ systematically from the participants in regard to demographic, socioeconomic, cultural, lifestyle, and medical characteristics, selection bias can occur.[146] Selection bias can also occur in studies that use data from registries. Only if selection into the study is associated with the exposure and the disease, selection bias manifests. Selection bias can increase or decrease the observed relationship between the exposure and the disease. Figure 1-7 depicts the concept of selection bias by means of a causal diagram. In the framework of causal inference, selection bias is defined as a consequence of *conditioning on a common effect* of exposure and outcome (or on a common effect of a cause of the exposure and a cause of the outcome). Within different settings, the concept of selection bias is known under many names: differential loss to follow-up, non-responder bias, missing data bias, volunteer bias, self-selection bias, healthy worker bias, Berkson's bias etc. The underlying causal concept, however, is the same.[149]

In case-control studies about mobile phone use and brain tumor risk, selection bias may occur, for example, if mobile phone owners are more likely to participate than persons who do not own a mobile phone. The control group is particularly vulnerable to selection bias in case-control studies as the motivation of the controls to participate may not be very high. Consequently, participation rates among controls are usually lower than among case patients. In INTERPHONE, for example, the participation rate for cases was 70% compared to only 53% among controls.[21] Such low participation rates among controls raise the question whether the control group is truly representative of the base population in terms of exposure. Indeed, mobile phone ownership was found to be lower among controls and cases that declined a participation in

INTERPHONE compared to those who participated.[153] In general, participation rates in case-control studies are declining which led to concerns about selection bias.[154-158] Specifically, participation rates in case-control studies about mobile phone use have ranged from 50% to over 90% among cases and 45% to 70% among controls.[153]

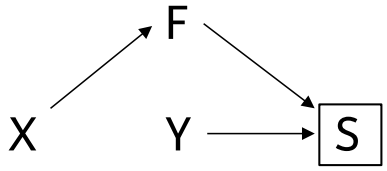

Figure 1-7 Directed acyclic graph (DAG) representing selection bias. X is the exposure, Y is the outcome, F is a measured covariate, and S is study participation (1=yes, 0=no). S is a collider (two arrows point to it) and therefore, no association (path) between X and Y exists. Because, however, the analysis is only done with individuals that were included in the study (S=1), the analysis is conditioned on S (represented by the box around S) and the path between X and Y is opened, introducing a spurious association between X and Y.

1.4.3.4 Information bias

Often, the methods or techniques for obtaining information about the subjects (about exposure and/or disease) are inadequate resulting in inaccurate information about the subjects.[146] If this inaccurate information is used to classify the subjects into discrete categories (e.g. in phone users and non-users), *exposure misclassification* can occur. The term *misclassification* is a synonym for measurement error for discrete variable.[149] If study participants have to recall their past exposure, *recall bias* may be introduced which refers to inaccurately recalled exposure (e.g. past mobile phone use). Information bias is called *non-differential* if the likelihood of misclassification or the level of recall bias does not differ between the groups being compared (e.g. cases and controls; Figure 1-8). In the case of a true exposure-response relationship, non-differential information bias will lead to risk estimates biased towards the null (no effect) if sub-

jects are classified into two categories (dichotomized). If, however, recalled exposure is used to classify the subjects into more than two categories (i.e. polytomous), non-differential misclassification can lead to either de- or increased risk estimates.[152,159-161] If the likelihood of misclassification or the level of recall bias differs between the groups under study, the information bias is *differential* (Figure 1-9). Differential information bias can lead to bias of the observed effect either towards or away from unity. Reverse causality exists when the outcome precedes the measurement of the exposure and is itself causally linked to the measured exposure.[149] Reverse causality (or reverse causation bias) is a type of measurement bias and has the same structure.

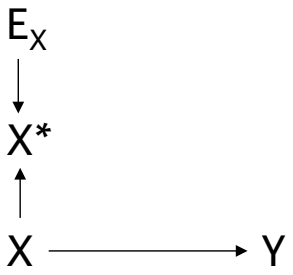

Figure 1-8 Directed acyclic graph (DAG) representing *non-differential* independent information or measurement error. X is the unknown true exposure, Y is the known outcome (here assumed to be measured without error) and X* is the reported or measured exposure and E_X represents all factors other than X that determine the value of X* (i.e. E_X = measurement error of X).

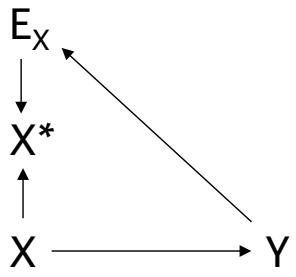

Figure 1-9 The same directed acyclic graph (DAG) as in Figure 1-8 except that the outcome Y is now causally related to the measurement of X*. If the outcome (e.g. being case patient with a brain tumor) influences the measurement of X* via E_X or directly, *differential* recall bias exists. If the measurement of the exposure occurs after the onset of the outcome, the resulting bias is called reverse causation bias or simply reverse causality.

Some studies compared self-reported mobile phone use with either objective records from network operators, from traffic data recorded by software modified phones (SMP) or hardware modified phones (HMP).[57,112,162-168] These studies found that recall of past mobile phone use is afflicted with large random and moderate systematic errors even if the recall period is as short as six months.[166] In general, the recall of number of calls was found to be more accurate than the recall of call duration.[162-166] Little evidence was found, on the other hand, for a difference in the amount of recall errors between cases (i.e. differential recall errors).[165]

1.5 Brain tumors

1.5.1 General aspects of carcinogenesis

The biological mechanisms of carcinogenesis are complex and still not fully understood.[169,170] Cancer is thought to be a multifactorial, chronic disease with multiple stages in its development. For cancer to develop, a mutation in a somatic cell is need-

ed. The time interval between initiation of exposure to the causal agent (initiator) and initiation of the disease is called *induction period.*[20] The interval between initiation of the tumor and its clinical emergence (e.g. appearance of manifestations) or to tumor detection is called *latency period.* The last step in carcinogenesis where the tumor grows is called tumor progression.

1.5.2 Incidence, incidence rate trends and survival

Brain tumors account for less than 2% of all malignancies worldwide.[171] The incidence of brain tumors is slightly higher among men than women and varies from 6–8/100'000 person-years (PY) in most countries in America, Europe and Oceania to 2–3/100'000 PY in Africa and Asia. The incidence in the general population is around 10–15/100'000 PY.[172] The age distribution of brain tumors shows a bimodal shape with a peak incidence in children and a second larger peak in adults aged 45–70.[171]

The incidence rate of acoustic neuroma (i.e. vestibular schwannoma, a benign tumor of the eighth cranial nerve) is estimated to be 10.4 per million person-years in the US during 2004–2007.[173] Incidence rate estimates from Denmark were about 20 per million person-years.[174] These differences in incidence rates are possibly due to variation in completeness of reporting of acoustic neuroma.

Among children, brain tumors are the second most common tumor type after leukemia.[175] Brain tumors account for approximately 25% of childhood cancer deaths and thus, are the leading cause of childhood cancer mortality.[47] The incidence of childhood brain tumors is about 3/100'000 PY between the age of 0–15 years.[176] About 1% of childhood brain tumors are present at birth or diagnosed within the first few months of life.[177] The majority of childhood brain tumors occur before the age of five years.[178,179]

Incidence rate trends of brain tumors tended to increase in most cancer registration areas in the late 1970s and early 1980s.[171] This increase is most likely to be accountable

to the improved diagnostic methods introduced during the same time period.[48,180] A large number of recent nationwide studies examined the incidence rate trends of brain cancer and found consistently no evidence for increasing brain tumor incidence rates over recent calendar years.[23,43-53] One study from Australia, however, reported statistically significantly increasing incidence rates between 2000 and 2008 of glioblastoma multiforme and meningioma, particularly after 2006.[54]

The 5-year relative survival for children aged 0–14 years increased modestly from 58% to nearly 63% in the period from 1975 to 1995 while that of young adults aged 14–55 years increased from 48% to 55%.[47] Survival for middle-aged adults (45–64 years) increased from 12% to 16% while it remained poor for the elderly aged ≥65 years (from 4% to 5%). 5-year survival rates differ substantially between tumor entities among children up to 17 years.[181] 5-year survival rate among children with astrocytoma increased from 66% in 1986[182] to 72% in 1998.[183] For medulloblastomas, 5-year survival increased from 36% in 1980–1984[184] to 41% in 1986[182] and to 41% in 1986.[183] For ependymomas, 5-year survival rates increased from 32% in 1986[182] to 51% in 1990[185] and to 64% in 1998.[183]

1.5.3 Tumor types

The brain is composed of two main cell types: neurons and glia cells. Both cell types arise in early development from the primitive neuroectoderm.[179] Glia cells are further divided into four categories: astrocytes, oligodendrocytes, ependymal cells, and microglia.[186] Most primary brain tumors emerge from glial cells and are further classified into groups such as glioblastoma, astrocytoma, oligodendroglioma, and ependymoma.[187] Meningiomas are mostly benign tumors that originate from the meninges. Meningiomas are the most common brain tumors among adults (20% among males and 38% among females) followed by glioblastomas (26% among males and 19% among females) and astrocytomas (15% among males and 12% among females).[188-190] The most common brain tumors among children are astrocytomas, which account for

approximately half of all childhood brain tumors followed by primitive neuroectodermal tumors (PNET, 21%), ependymomas (9%) and other gliomas (15%).[179] Among PNET, medulloblastomas are the most frequent. Brain tumors among children are much more likely to be malignant compared to adults (65.2% vs. 33.7%, respectively).[188] Supratentorial tumors (i.e. tumors above the tentorium cerebelli, an extension of the dura mater that separates the cerebellum from the occipital lobes) occur predominantly in the first two years and late adolescents whereas infratentorial tumors (i.e. tumors below the tentorium cerebelli) are more common during childhood.[191]

Acoustic neuroma is a benign tumor of the eighth cranial nerve that leads from the inner ear to the brainstem.[56] Acoustic neuromas constitute approximately 5% of intracranial tumors. All studies reported a sex ratio close to one.[173,174,192,193] The incidence rate shows a peak in the age group of 50–65 years olds.

Among adults, the incidence of meningioma is higher among females than males (ratio of f:m=2–3:1).[194,195] The incidence of glioma, on the other hand, is higher among males compared to females (ratio=1:1.5).[48,195]

In general, boys suffer more frequently from brain tumors compared to girls.[196-199] Incidences for astrocytoma do not substantially differ between girls and boys (ratio=1:1) whereas medulloblastomas (a form of PNET) are more frequent among boys compared to girls (ratio=1:1.5–2).[182,188,200,201]

1.5.4 Spatial distribution of radiofrequency energy in the brain

The physical measure describing the absorption of radiofrequency electromagnetic fields in biological tissue is the specific absorption rate (SAR). The unit of the SAR is watts per kilogram (W/kg). Lower SAR values mean that less radiation is absorbed by the tissue compared to higher SAR values.

The exposure to radiation from mobile phones is highly localized. Most of the radiation (i.e. 97–99%) is absorbed in the brain hemisphere on the side were the mobile phone is held (Figure 1-10).[202] The use of the mobile phone on the same side where the tumor later occurred is called *ipsilateral* use. In contrast, use of the mobile phone on the opposite side of the head where the tumor occurred is called *contralateral* use. Regarding the anatomical structures of the brain, the temporal lobe shows the highest absorption (50–60%) followed by the frontal lobe (14–19%) and the cerebellum (12–13%; Figure 1-11).

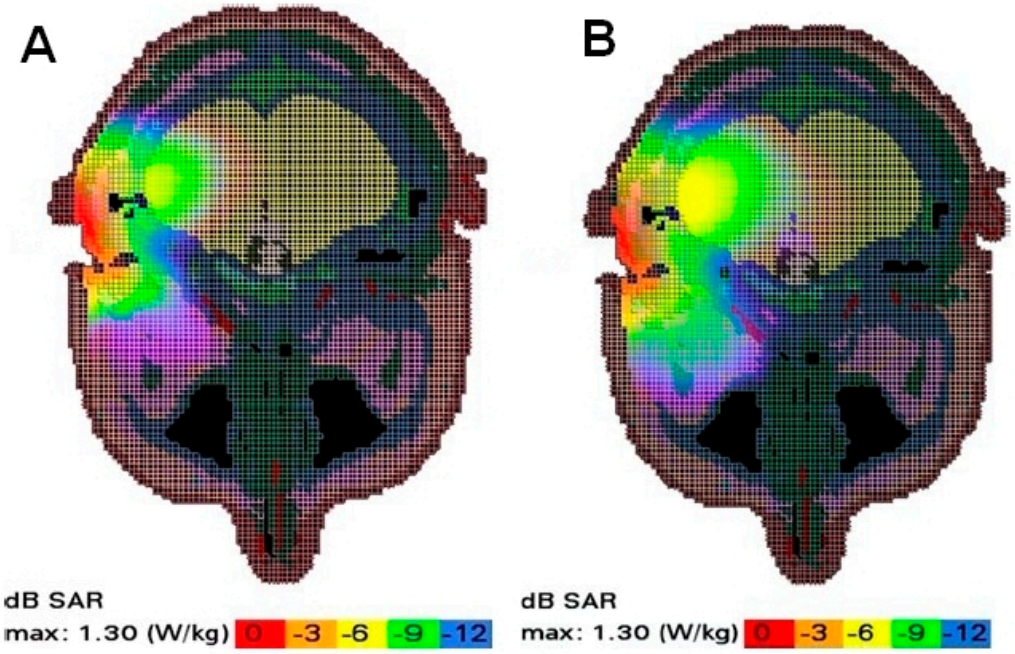

Figure 1-10 SAR distribution inside an adult (A) and child (B) human head model as seen from above.[203] The exposure is highly localized and mainly confined to the brain hemisphere on the side where the mobile phone handset is held (right side in this case). The radiation penetrates into deeper brain regions in the child (B) compared to the adult head (A).

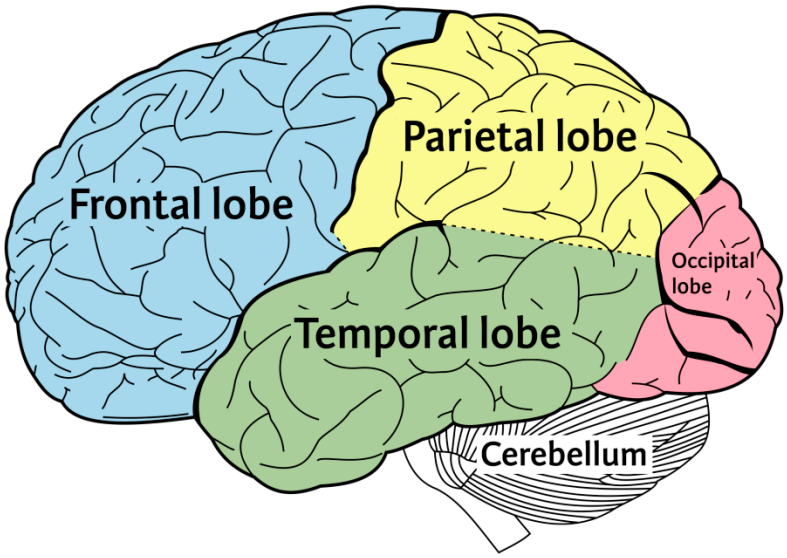

Figure 1-11 Lobes of the brain. Most radiation from mobile phones is absorbed in the temporal lobe (50–60%) followed by the frontal lobe (14–19%) and the cerebellum (12–13%).[202] Source: http://en.wikipedia.org/wiki/Cerebral_cortex, accessed 4. May 2012.

1.5.5 Etiology (causes)

Despite rigorous efforts to identify risk factors, the causes for adult and childhood brain tumors are largely unknown.[171,179,195,204] The only established non-genetic risk factor is therapeutic doses of ionizing radiation to the head.[171,179,195,200] Among children, therapeutic doses of ionizing radiation are usually administered for treatment of early childhood cancers and earlier, also for treatment of *tinea capitis*.[205-209] A few rare genetic syndromes are also known to increase the risk for childhood brain tumors. These syndromes include neurofibromatosis, Li-Fraumeni syndrome (inherited *p53* mutations), basal cell nevus (Gorlin's) syndrome, Turcot syndrome, ataxia telangiectasia and tuberous sclerosis.[179,195,200,210] Yet less than 5% of all brain tumors can be attributed to all these known causes together. In addition, different brain tumor sub-

types are likely to have different causes. The molecular pathways leading to malignant astrocytoma on the one hand and benign meningiomas and acoustic neuromas on the other are different.[211] It is currently thought that brain tumors occur over decades after tumorigenic exposures early in life.[19] The latency period of tumors varies from months to years depending on the aggressiveness of the tumor growth and the location of the tumor.

Numerous risk factors have been proposed to alter the risk of brain tumors among children[179,212] as well as adults[213] but there is inconclusive, minimal, or no evidence for a causal relationship for most of the proposed factors. Suggested associations include: head injury and trauma, family history of brain tumors, female sex hormones and reproductive factors, prior cancer, epilepsy and seizures, traffic related air pollution, alcohol, infections, maternal and paternal smoking, maternal diet (especially cured meat), *N*-nitroso compounds, maternal age and birth characteristics such as birth weight or birth order, exposure to pesticides and farm-related exposures, allergic conditions (e.g. asthma, atopy), paternal occupation and hobbies, maternal medication and vitamin intake during pregnancy, socioeconomic factors, electromagnetic fields, as well as electromagnetic fields from mobile phones. For most of the proposed risk factors, studies yielded inconclusive and conflicting results and often face methodological limitations that prevent a causal interpretation.[179] Table 1 provides a concise review of the literature concerning possible risk factors of brain tumors.

Table 1 Review of the literature concerning possible risk factors for brain tumors.

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Therapeutic doses of ionizing radiation	DNA damage, ionization of molecules.	Increasing	Strong evidence for causal relationship. Established strong risk factor.	171,179,195,200,214-216
In utero exposure to ionizing radiation	DNA damage, ionization of molecules.	Increasing	Strong evidence for causal relationship.	179,217
Genetic syndromes (see section 1.5.5 for a list of syndromes)	Depends on syndrome.	Increasing	Strong evidence for causal relationship. Established strong risk factor.	179,195,200,210,214

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Reproductive and menstrual factors/Female sex hormones	Progesterone, androgen, estrogen. Mechanism unknown.	Increasing risk for meningioma, decreasing risk for astrocytomas.	Inconclusive and inconsistent results from rather small, low-powered studies. For meningioma and astrocytoma, estrogens and maybe other hormones may alter risk. Evidence from cohort studies needed.	[218-232]
Family history of brain tumors	Genetic etiology, common exposure to environmental agents.	Increasing	Conflicting evidence. Evidence suggests environmental causes. 5% of gliomas are estimated to be familial.	[233-238]

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Prior cancers	Common environmental or susceptibility factors.	Increasing	Evidence for relationship with: breast cancer (meningioma among women), colorectal cancer, small-cell lung carcinoma, adenocarcinoma.	[238-241]
Head injury and trauma	Increased cell division leading to mutations.	Increasing	Conflicting and inconclusive evidence. Minimal evidence for causal relationship.	[214,242-252]
Traffic-related air pollution	Carcinogenic compounds in traffic exhaust.	Increasing	No evidence for increased risk of brain tumors. Scientific literature is scarce.	[253]

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Alcohol	*N*-nitroso compounds or precursors thereof. Otherwise unknown.	Increasing	Inconsistent evidence. Modest risk estimates.	187,254-256
Epilepsy and seizures	Unknown	Increasing	Established relationship although evidence suggests that epilepsy and seizures are rather symptoms than causes of brain tumors.	214,238,257-263
Toxoplasma gondii	Unknown	Increasing	Evidence for meningioma, conflicting evidence for glioma. Cohort study with serologic measurement of bacterial exposure needed.	256,264-266

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Human polyoma-viruses (SV40, JCV, BKV)	Viral proteins dysregulate cellular pathways of the cell cycle, DNA repair, and others.	Increasing	Evidence for relationship but conflicting results and inadequate study methodology prevent a causal interpretation up to date. Cohort study with serologic measurement of viral exposure needed.	214,267-275

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Chicken pox (varicella zoster virus)	Unknown	Protective	Evidence for protective effect of immunity to and/or clinical manifestations of varicella-zoster virus and glioblastoma. Cohort study with serologic measurement of viral exposure needed.	195,214,276,277
Influenza/Cold	Unknown	Protective	A history of cold or influenza infection appears to decrease glioma risk. Cohort study with serologic measurement of viral exposure needed.	214,261,278,279

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Maternal and paternal smoking	*N*-nitroso compounds and other compounds that penetrate the blood-brain barrier.	Increasing	Inconsistent evidence and the magnitudes of the effect estimates are modest.	280-287
Cured meat	*N*-nitroso compounds.	Increasing	Conflicting evidence. Methodological limitations of current studies prevent a causal interpretation.	214,283,288-291

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Maternal age and intrauterine and neonatal characteristics (e.g. weight, birth order, head circumference)	Unknown	Increasing for increasing maternal age, high birth weight, higher head circumference, small- and large-for gestational age, premature birth, apgar score, beech presentation and decreasing for birth order.	Evidence for increased risk of CNS tumors with increasing maternal age, small- and large-for-gestational age, high birth weight (astrocytomas), higher head circumference, born prematurely, low apgar score (<7) and beech presentation. Evidence for decreasing risk for brain tumors with increasing birth order.	214,292-297

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Pesticides and farm-related exposures	*N*-nitroso compounds and other chemical exposures. Animal viruses (avian sarcoma virus, adenoviruses, polyomaviruses).	Increasing	Evidence for increased risk for farm-related maternal exposure (pigs, horses, poultry). Conflicting evidence for exposure to pesticides.	214,298-303

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Paternal occupation and hobbies	Alteration of sperm cells. Polycyclic Aromatic Hydrocarbons (PAHs) and other solvents. Paternal exposure to pesticides.	Increasing	Evidence for increased risk for the following paternal occupations: painter, exposure to pesticides (agriculture), motor-vehicle-related occupations. Evidence for paternal exposure to PAHs and brain tumor risk in offspring.	214,304-308

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Maternal medication and vitamin and micronutrient intake during pregnancy	*N*-nitroso compounds from nitrosatable drugs (e.g. antihistaminics, aspirin, and antibiotics). Otherwise unknown.	Increasing for nitrosatable drugs, decreasing for multivitamins, iron and folate intake.	Evidence for increased risk for diuretics and other antihypertensives. Conflicting evidence for vitamin, folate or iron supplementation. No evidence for increased risk for pain relievers, antinauseants, or cold medications.	[214,309-312]
Socioeconomic factors	Unknown	Increasing	Conflicting and inconclusive evidence for causal relationship.	[214,313-319]

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Allergic conditions (asthma, atopy)	Enhanced tumor immunosurveillance. Not yet fully understood.	Protective	Consistent evidence for a protective effect.	214,260,261,282,320-331
Electromagnetic field exposure (occupational and residential)	Unknown	Increasing	Inconsistent evidence for an increased brain tumor risk (neither occupational nor residential). Methodological limitations of the studies prevent a causal interpretation.	214,332-338

Risk factor(s)	Possible mechanism/ carcinogenic agents	Assumed direction of effect on brain tumor risk	Summary of evidence	References
Mobile phones	Unknown	Increasing	Fairly consistent evidence against a relationship for short-term use of mobile phones. Uncertainties for long-term (>10–15 years) and heavy use. Brain tumor incidence rates remained stable despite the heavy increase of mobile phone use.	21,30,31,34,41,43,45,46,50,56,60,81,136,339

2 Framework and objectives

2.1 The CEFALO project

This thesis is part of the CEFALO project. CEFALO (from the Greek word kephale, head) is a multicenter case-control study about mobile phone use and brain tumors in children and adolescents. The aim of CEFALO was to assess whether or not there is a relationship between mobile phone use and the development of brain tumors in children and adolescents. Participating countries were Sweden, Denmark, Norway, and Switzerland. In addition to the exposure to mobile and cordless phones, other potential risk factors for brain tumors were also studied. Other factors included the medical history of the child, pregnancy and birth related factors, contact with animals and farm-life, and allergies of the child and family.

2.2 Aims of this thesis

Aim 1: Assess how recall errors and selection bias influence the risk estimates in case-control studies about mobile phone use and brain tumors in children and adolescents.

Recall errors and selection bias are a common problem in case-control studies. Since the recall of past mobile phone use has been shown to be imprecise, we conducted a simulation study where we assessed the impact of random and systematic recall errors and of selection bias on the result of case-control studies about mobile phone use and

brain tumor in children and adolescents. We used operator-recorded traffic data that were available for a subset of the CEFALO participants to compare self-reported and operator-recorded mobile phone use (validation). The results of the comparison were then used to calculate plausible values of recall errors and of selection bias. In a simulation, we generated two hypothetical case-control datasets with mobile phone users and non-users. The proportion of mobile phone users was guided by the observed proportion of mobile phone users in the CEFALO study sample. We assigned a level of exposure (i.e. cumulative number of calls) to each mobile phone user by sampling from a log-normal distribution. A logistic function was then used to calculate a probability to become a brain tumor patient. In the first of the simulated case-control datasets, we assumed that there is no relationship between mobile phone use and the risk of brain tumors (OR=1, no-risk scenario). In the second dataset, we assumed an odds ratio of 1.5 per 10'000 cumulative number of calls (risk scenario). For each scenario of levels of recall errors and selection bias, 5000 samples each containing 353 case patients and 646 controls were repeatedly drawn from the generated two case-control datasets. Recall errors and selection bias were studied separately. To simulate random and systematic recall errors, we multiplied the generated cumulative number of calls by a factor drawn from a log-normal distribution in order to get the observed number of calls. A factor greater than one denotes overestimation while a factor lower than one denotes underestimation of cumulative number of calls. The 10th and 75th percentile of the observed cumulative number of calls were then used to categorize the subjects into non-regular users (below the 10th percentile), regular users (10–75th percentile), and heavy users of mobile phones (above the 75th percentile). By variation of the factor with which the assigned exposure was multiplied, we could implement various scenarios of random and systematic recall errors. If the mean of the distribution of the multiplicative error factor was one, no systematic but only random recall errors were generated. A mean of the distribution of the multiplicative error factors greater or lower than one denoted systematic under- or overestimation, respectively. To simulate selection bias, we varied the probabilities of users and non-users of mobile phones to be drawn from the case-control datasets. In addition, we studied plau-

sible scenarios for CEFALO based on the results of the comparison between self-reported and operator-recorded mobile phone use. In these scenarios, we combined recall errors and selection bias. The results of this study are presented in article 1.

Aim 2: Determine factors that predict the level and the overestimation of mobile phone use among children and adolescents.

Many studies about mobile phone use and health outcomes in children and adolescents rely on the participants' self-reported mobile phone use as exposure. The results of these studies must be interpreted with caution, due to substantial reporting error.[163] So far it is not clear whether poor estimation of own mobile phone use is associated with specific health-related characteristics of the study participants. Such factors could result in confounding and should be considered in the statistical analyses. We assessed possible predictors of level of mobile phone use and explored factors that are related to overestimation (i.e. ≥50% overestimation) of mobile phone use using data from CEFALO. We used objective operator-recorded data from Denmark, Sweden and Switzerland to compare self-reported with operator-recorded amount of mobile phone use. Many variables were considered to serve as predictors of overestimation of recalled mobile phones: country, health status (case, control), age (7–14, 15–19 years), gender, socioeconomic status of the parents (low, intermediate, high), time between reference date and interview (<1.5 years, ≥1.5 years) and amount of operator-recorded phone use (tertiles served as cut-offs). The results of this study are presented in article 2.

Aim 3: Evaluate if mobile phone use is related to brain tumor risk in children and adolescents.

All children and adolescents aged 7–19 years from Sweden, Denmark, Norway and Switzerland who were diagnosed with a primary brain tumor between 2004 and 2008 were included in CEFALO. For each case patient, we selected two healthy control subjects using population registries matched by age, sex and geographical region of residence. Exposure data was collected by face to face interviews with the study participants accompanied by at least one parent (preferably the mother). All study participants were asked if they had ever spoken on a mobile phone more than 20 times during their lives and if the child ever owned a mobile phone before the diagnosis date. Owners of a mobile phone were asked how many subscriptions they have had and for each subscription, the following information was asked: start and end date, use of hands-free devices, preferred side of the head during use, number of calls per day, and duration of calls (both in predefined categories of use). Risk estimates for brain tumors were calculated for regular use of mobile phones (defined as at least one call per week for at least six months or more), time since first use of mobile phones, cumulative duration of subscriptions, cumulative duration of calls, and cumulative number of calls. In addition, we also analyzed brain tumor risk for ipsi- and contralateral use of mobile phones as well as for the parts of the brain that are known to receive most of the radiation during a phone call. Numerous stratified and sensitivity analyses were calculated to evaluate the consistency of our findings. Furthermore, we examined the gender and age-adjusted brain tumor incidence rates among Swedish children and adolescents aged 5–19 years from 1990 to 2008 including hypothetical incidence rate trends based on the risk estimates found in our analyses. The results of CEFALO are presented in article 4.

3 Recall of mobile phone use and exposure assessment

3.1 Article 1: Impact of recall errors and selection bias in case-control studies

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Impact of Random and Systematic Recall Errors and Selection Bias in Case–Control Studies on Mobile Phone Use and Brain Tumors in Adolescents (CEFALO Study)

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Whether the use of mobile phones is a risk factor for brain tumors in adolescents is currently being studied. Case–control studies investigating this possible relationship are prone to recall error and selection bias. We assessed the potential impact of random and systematic recall error and selection bias on odds ratios (ORs) by performing simulations based on real data from an ongoing case–control study of mobile phones and brain tumor risk in children and adolescents (CEFALO study). Simulations were conducted for two mobile phone exposure categories: regular and heavy use. Our choice of levels of recall error was guided by a validation study that compared objective network operator data with the self-reported amount of mobile phone use in CEFALO. In our validation study, cases overestimated their number of calls by 9% on average and controls by 34%. Cases also overestimated their duration of calls by 52% on average and controls by 163%. The participation rates in CEFALO were 83% for cases and 71% for controls. In a variety of scenarios, the combined impact of recall error and selection bias on the estimated ORs was complex. These simulations are useful for the interpretation of previous case–control studies on brain tumor and mobile phone use in adults as well as for the interpretation of future studies on adolescents. Bioelectromagnetics 32:396–407, 2011. © 2011 Wiley-Liss, Inc.

Key words: mobile phones; brain tumors; adolescents; recall error; selection bias

INTRODUCTION

There has been a steep increase in the ownership of mobile phones and the amount and duration of their use throughout the world since the 1990s [Böhler and Schüz, 2004; Schüz, 2005; Mezei et al., 2007]. The ubiquitous presence of wireless telecommunication devices raised concerns about possible adverse health effects of radio frequency fields produced by such devices. Due to the proximity of mobile phones to the head during calls, tumors of the brain, acoustic nerve, and salivary glands have been the primary concerns [Cardis et al., 2008], giving rise to many studies that concentrated on the possible relationship between mobile phone use and brain tumors [Ahlbom et al., 2009; INTERPHONE Study Group, 2010]. The current scientific consensus is that there is little evidence of

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adverse health effects from mobile phones [Ahlbom et al., 2009]. However, this evidence arose mainly from case–control studies conducted on adults.

In case–control studies dealing with mobile phones and brain tumors, the degree of exposure is assessed retrospectively, relying primarily on self-reported mobile phone use assessed in personal interviews or by questionnaires. Self-reported data on past exposure to mobile phones are therefore prone to error, which may result in exposure misclassification. Throughout the manuscript, we use the term ''recall error'' for errors in the exposure data irrespective of the source of information. Recall errors can either occur at random so that the average of the recall errors is zero or there can be systematic recall errors where the average error differs from zero, that is, under- or overestimation of the exposure. If the direction or extent of random or systematic recall errors differs between cases and controls, we use the term ''differential'' [Vrijheid et al., 2006; Rothman et al., 2008].

Another error source apparent in case–control studies requiring personal contact with study subjects is selection bias. Selection bias occurs if the probability to participate in the study is related to the health status and to the exposure. In a large multinational case–control study on mobile phone use and brain tumors in adults (INTERPHONE), Vrijheid et al. [2009b] found that there were less mobile phone users among non-participants than among participants. This is expected to introduce selection bias as overall participation rates were shown to be higher in cases than in controls.

This paper investigates the effects of random and systematic recall error and of selection bias in case–control studies of mobile phone use and brain tumor risk in children and adolescents through sensitivity analyses using Monte Carlo computer simulations. To parameterize our models, we used real data on response rates and network operator-recorded mobile phone use from CEFALO. Furthermore, we assessed the impact of recall error and selection bias on categorical relative risk estimates in the upcoming CEFALO study, an international case–control study investigating the relationship of mobile phone use and brain tumors in children and adolescents aged 7–19 years in Denmark, Norway, Sweden and Switzerland.

METHODS

Study Design

In 2006, CEFALO, an international case–control study of the association between the use of mobile telephones and the risk of brain tumors among children aged 7–19 years had been set up in Denmark, Norway, Sweden, and Switzerland. Eligible cases were all children diagnosed during the study period with intracranial central nervous system (CNS) tumors, who were between the ages of 7 and 19 years at the time of diagnosis. Two controls were randomly selected from a population register of the total population of the study area, stratified by age, gender, and residential area. Controls that refused to participate in the study were asked to complete a short non-responder questionnaire.

Comparison of Self-Reported Mobile Phone Use and Network Operator Records

Data from two mobile phone network operators in Sweden and from three network operators in Denmark were compared with the self-reported mobile phone use from the CEFALO study. In CEFALO, the amount of mobile phone use was assessed by face-to-face interviews with the child accompanied by its parents (preferably the mother). On average, cases were interviewed 844 days after the reference date while the corresponding time for controls was 886 days. We used self-reported information about the number of calls (6 pre-determined categories ranging from $<$1/week to $\geq$5/day) and duration of calls (4 categories ranging from $\leq$1 to $\geq$10 min/call) as well as information about the length of the corresponding usage period in months to calculate the cumulative number and duration of mobile phone calls for each study participant. We used the midpoint of the categories to calculate continuous exposure measures (e.g., we used 1.5 calls/week if a participant checked the category 1–2 calls/week). If a participant checked the lowest or the highest category that did not have a midpoint, we used 2 calls/month or 7 calls/day, respectively.

Data from network operators were available for 59 cases (26% of all cases that own a mobile phone) and 91 controls (22% of all controls that own a mobile phone). From the network operators, we received information about the number of calls, the duration of calls as well as the subscription start and end dates. Network operator records were only included if data from both the subject and the network operator were available, and if the subject could be clearly linked to the network operator record through a specific personal identification number, phone number, name, or any combination of these data given by the study participants. Periods of reported mobile phone use were matched to operator-recorded periods for each subject. If the overlap between self-reported subscription periods and operator-recorded subscription periods were incomplete, the total number and duration of calls for the corresponding subscription period were corrected by multiplication with the proportion of overlapping time. We only considered use of mobile phones prior to the reference date (defined as

date of diagnosis of the case in each matched set). The level of agreement between self-reported and operator-recorded phone use was measured by the ratio of self-reported to operator-recorded phone use [Vrijheid et al., 2009a]. The median of this ratio represents the average level of systematic under- or overestimation while the interquartile range (IQR) of the ratio represents the variation between individuals, which is a measure of the random recall error. We present the median and IQR of the ratios. All calculations were done on the log scale and results were then back-transformed.

We calculated the ratio of reported to recorded mobile phone use separately by country, gender, age group (7–14 and 15–19 years), reported years since first use (0–50th, 50–75th, >75th percentiles of controls that were regular users) and the operator-recorded cumulative number and duration of calls (0–50th, 50–75th, >75th percentiles of controls that were regular users).

We used the Mann–Whitney *U*-test to assess whether the overall median of the ratio differed between cases and controls [Mann and Whitney, 1947].

Recall Error Model

We used a multiplicative error model to simulate the effects of random and systematic recall errors [Vrijheid et al., 2006]. The recall error model was of the form:

$$X_{\text{obs}} = X_{\text{true}} \times \varepsilon$$

where X_{obs} denotes the observed exposure, X_{true} denotes the true assigned exposure, and ε denotes the multiplicative recall error term. The multiplicative recall error term ε follows a log-normal distribution and can be interpreted as the ratio of self-reported to actual mobile phone use described above. When ε is 1, this means that there is no recall error while values of $\varepsilon < 1$ or >1 denote under- and overestimation of mobile phone use, respectively. We used the exposure distribution of mobile phone users among controls in CEFALO to categorize the exposure. Subjects with an observed exposure (X_{obs}) below the 10th percentile were classified as non-regular users of mobile phones. Users of mobile phones with an observed exposure between the 10th and 75th percentiles were classified as regular users, and users with exposure exceeding the 75th percentile were classified as heavy users. Note that heavy users were also regular users. The proportion of nonusers was 36% in the simulated dataset as observed in the CEFALO study.

Design and Analysis Methods

We investigated the influence of random and systematic recall errors and of selection bias on cancer risk estimates by repeated sampling from a large case–control dataset that resembled central characteristics of the CEFALO study population. Thereby, we assumed true odds ratios (OR) of 1 (no risk scenario) and 1.5 (risk scenario) per 10,000 cumulative number of calls for all scenarios described below.

Recall Error Scenarios

We studied random and systematic recall errors separately. In addition, we included three scenarios that combined random and systematic recall errors. (1) Random recall errors: Under these scenarios, we assumed that there was no systematic under- or overestimation present. Therefore, we kept the mean of the recall error distribution ε at 1 but allowed the standard deviation of ε to vary. Specifically, we allowed the standard deviation of the recall error distribution to take the following values: 0 (no random recall error), 0.5, 1.0, 1.5, and 2.0. (2) Systematic recall errors: In contrast to the preceding scenarios, we assumed that there was a systematic under- or overestimation present but no variation between the subjects. This corresponds to the fact that we allowed the mean of the measurement error distribution ε to vary while we fixed the standard deviation of ε at 0. Specifically, we considered under- and overestimations of -50, -10, 0 (no systematic recall error), 10%, 50%, and 100% corresponding to means on the log-scale of -0.7, -0.1, 0, 0.1, 0.4, and 0.7, respectively. (3) Combined recall errors: In the combined recall errors scenarios, we incorporated random and systematic recall errors at the same time in our models. We combined under- and overestimations of -50% and 100% with standard deviations of 1 and 2, respectively.

Selection Bias

To simulate the effects of selection bias on the ORs for regular and heavy users of phones, we considered five different combinations of participation probabilities for the users and nonusers of mobile phones among cases and controls with participation probabilities ranging from 0.4 to 0.8. We chose this range because it covers the participation rates that were seen in studies about mobile phone use and brain tumor among adults [Inskip et al., 2001; INTERPHONE Study Group, 2010].

Plausible Scenarios for CEFALO

We based the plausible scenarios for CEFALO on the results of the comparison between self-reported and operator-recorded mobile phone use in our data and used three different combinations of observed recall errors and selection bias. Our choice of the participation probabilities was guided by 63 non-responder

questionnaires of controls enrolled in CEFALO. For cases, virtually no non-responder questionnaires were available. For controls, we used a logistic regression model to assess the participation probabilities of users and nonusers of mobile phones with the participation as dependent variable and the answer of the question if the subject ever used a phone more than 20 times as independent variable. We adjusted the estimate for country and age.

Generation of the Case–Control Dataset

We used a modified procedure described by Vrijheid et al. [2006] to generate a case–control dataset. In particular, we used a loop to generate the cases and controls. First, we used a Bernoulli distribution with the observed parameter $P = 0.64$ to determine whether a subject is a user of mobile phones or not. If a subject was a user, we assigned a level of exposure (i.e., cumulative numbers of calls) by sampling from a log-normal distribution which parameters were inferred from the distribution of controls in the operator-recorded data. We assigned an exposure of 0 to nonusers. We based the probability of a nonuser to become a case on the incidence rate observed in the CEFALO study. CEFALO enrolled 423 eligible brain tumor cases that originated from a population containing around 4 million 7- to 19-year-old children and adolescents in Denmark, Norway, Sweden and Switzerland. We assigned each subject (i) a probability (P) of disease ($D = 1$) corresponding to the logistic function:

$$P(D_{\mathrm{i}} = 1|X_1; \beta, \alpha) = (1 - P(D_{\mathrm{i}} = 1|X_{\mathrm{i}} = 0)) \times \frac{e^{(\alpha+\beta\times X_i)}}{(1 + e^{(\alpha+\beta\times X_i)})}$$

The parameter α was set to obtain the observed incidence rate of brain tumors in CEFALO. The parameter e^{β} corresponds to the true OR. In the next step, we used a Bernoulli distribution with the calculated probability P to determine if a subject was a case or a control. The user status, the exposure and the health status were stored until 10,000 cases and 4 million controls were generated. From the generated case–control dataset, we repeatedly drew a random sample consisting of 352 cases and 646 controls for further analyses. We repeated the sampling from the generated dataset 5,000 times for each scenario to ensure robust estimation. We calculated the ORs for regular and heavy use with the combined number of nonusers and non-regular users of phones as a reference group for each of the 5,000 repetitions under each scenario considered. For presentation, we calculated the median of the simulated ORs across the 5,000 repetitions as well as the 2.5th and the 97.5th percentiles. We used the R software program version 2.11.0 [R Development Core Team, 2010] for all simulations.

RESULTS

In total, 423 cases and 909 potential controls were identified during the study period of CEFALO. Interviews were completed with 352 (83.2%) eligible cases and 646 (71.1%) eligible controls. For 63 eligible controls that did not participate in CEFALO, a non-responder questionnaire was completed.

Assuming a true OR per 10,000 cumulative numbers of calls of 1.5 (risk scenario), we found unbiased ORs on the categorical scale to be 1.17 (0.91–1.54) for regular use and 1.52 (1.06–2.17) for heavy use.

Comparison of Self-Reported Mobile Phone Use and Operator Records

Both self-reported and operator-recorded data were available for 48 cases and 86 controls. For 36 (75%) cases and 63 (73%) controls, the operator-recorded subscription periods did not cover the self-reported subscription periods completely. For cases, the operator-recorded subscription periods covered 63% of the self-reported subscription periods on average, while the corresponding figure for controls was 69%. Overall, 39 (45%) controls and 20 (42%) cases were male and 46 (53%) controls and 24 (50%) cases were 7–14 years old. The median and IQR of the operator-recorded cumulative number of calls was 905 and 1,420 for the cases and 774 and 1,397 for the controls, respectively. The corresponding median and IQR values for the operator-recorded cumulative duration of calls (min) were 1,241 and 1,885 for the cases and 887 and 2,076 for the controls, respectively. On average, both cases and controls overestimated the cumulative number of calls and the cumulative duration of calls (Table 1). Cases overestimated their number of calls by 9% on average and controls by 34%. There was little evidence that the median overestimation differed between cases and controls (Mann–Whitney U-test, $P = 0.20$). Cases overestimated their duration of calls by 52% and controls by 163%. There was borderline significant evidence that overestimation of duration was more pronounced in controls than in cases (Mann–Whitney U-test, $P = 0.07$). When we combined cases and controls, the median ratio of self-reported cumulative number of calls divided by the operator data was 1.23 (0.53–3.75) while the corresponding ratio was 2.20 (0.78–8.04) for the duration of calls. In general, the overestimation of mobile phone use decreased with increasing cumulative operator-recorded phone use

TABLE 1. Results From the Validation Study Show Ratios of Self-Reported to Operator-Recorded Mobile Phone Use

	Cases				Controls			
	N	Number of calls	*N*	Duration of calls	*N*	Number of calls	*N*	Duration of calls
Overall	48	1.09 (0.47–2.27)	48	1.52 (0.70–4.28)	86	1.34 (0.63–5.36)	86	2.63 (0.89–10.06)
By country								
Denmark	20	0.87 (0.40–1.41)	20	2.21 (0.83–7.40)	29	1.03 (0.45–1.62)	29	2.07 (0.92–8.21)
Sweden	28	1.26 (0.51–2.94)	28	1.08 (0.63–4.18)	57	1.55 (0.85–6.19)	57	2.93 (0.89–10.06)
By gender								
Male	20	1.09 (0.60–2.86)	20	1.27 (0.71–3.93)	39	1.15 (0.49–4.50)	38	1.55 (0.53–8.84)
Female	28	1.03 (0.39–2.27)	28	2.55 (0.69–4.49)	47	1.48 (0.72–6.46)	48	3.13 (1.30–10.19)
By age (years)								
7–14	24	1.15 (0.52–1.85)	24	1.08 (0.65–3.00)	46	1.24 (0.47–3.49)	45	1.69 (0.67–4.59)
15–19	24	0.99 (0.41–2.58)	24	3.08 (0.80–7.60)	40	1.52 (0.94–6.33)	41	4.93 (1.02–14.80)
By reported years since first use (regular users only)								
0–3.6	21	1.11 (0.53–1.31)	21	0.99 (0.63–3.12)	41	1.30 (0.47–5.36)	41	1.95 (0.77–8.21)
3.7–5.3	12	0.45 (0.36–1.80)	12	1.54 (0.50–5.57)	25	1.47 (0.85–4.50)	25	3.34 (1.44–10.06)
5.4–15.1	15	1.89 (0.91–3.75)	15	2.99 (1.14–5.52)	20	1.63 (0.84–5.40)	20	2.83 (0.80–13.06)
By operator-recorded usage (regular users only)								
1st quartile (<25%)	12	1.15 (0.41–5.06)	12	4.34 (0.83–10.40)	22	6.12 (0.75–28.76)	22	5.83 (1.69–15.54)
2nd and 3rd quartile (25–75%)	16	1.02 (0.47–1.69)	16	1.23 (0.65–2.55)	32	1.42 (0.59–5.07)	31	2.17 (0.92–9.75)
4th quartile (>75%)	12	0.87 (0.52–2.08)	14	1.90 (0.62–4.09)	16	1.25 (0.41–2.50)	17	2.23 (1.10–9.18)

Given are medians and the interquartile range in parentheses.

and increased with increasing reported years since first use in both cases and controls.

Recall Errors

Random recall errors. The simulated OR for regular use increased with increasing random recall errors of controls and decreased with increasing random recall errors of cases (Table 2). These findings were independent of the true OR. The opposite pattern was found for heavy users when we assumed no risk of mobile phones, whereas the pattern was complex when we assumed a true OR of

TABLE 2. Effects of Random Recall Errors on the Odds Ratio (OR) for Regular Use and Heavy Use

			SD cases				
	Unbiased OR	SD controls	0.0	0.5	1.0	1.5	2.0
Regular use	1.00	0.0	1.01 (0.78–1.30)	0.97 (0.74–1.26)	0.88 (0.68–1.13)	0.80 (0.62–1.05)	0.71 (0.55–0.91)
	1.00	0.5	1.04 (0.80–1.33)	1.00 (0.77–1.29)	0.92 (0.71–1.19)	0.82 (0.64–1.07)	0.74 (0.57–0.96)
	1.00	1.0	1.13 (0.87–1.45)	1.08 (0.84–1.40)	1.01 (0.78–1.30)	0.90 (0.70–1.17)	0.81 (0.63–1.05)
	1.00	1.5	1.21 (0.93–1.56)	1.18 (0.91–1.54)	1.11 (0.86–1.45)	1.01 (0.77–1.30)	0.89 (0.70–1.16)
	1.00	2.0	1.28 (0.99–1.65)	1.24 (0.96–1.62)	1.20 (0.92–1.57)	1.10 (0.86–1.43)	1.01 (0.79–1.31)
	1.17	0.0	1.18 (0.91–1.54)	1.13 (0.87–1.48)	1.04 (0.80–1.34)	0.96 (0.74–1.25)	0.82 (0.64–1.06)
	1.17	0.5	1.23 (0.94–1.59)	1.17 (0.90–1.53)	1.07 (0.83–1.38)	0.97 (0.74–1.25)	0.88 (0.68–1.14)
	1.17	1.0	1.31 (1.01–1.71)	1.28 (0.98–1.67)	1.16 (0.90–1.51)	1.05 (0.81–1.37)	0.97 (0.75–1.26)
	1.17	1.5	1.42 (1.08–1.86)	1.37 (1.06–1.80)	1.27 (0.98–1.66)	1.18 (0.90–1.54)	1.07 (0.83–1.40)
	1.17	2.0	1.47 (1.13–1.93)	1.44 (1.11–1.89)	1.37 (1.06–1.79)	1.28 (0.98–1.69)	1.19 (0.91–1.55)
Heavy use	1.00	0.0	0.99 (0.66–1.43)	1.01 (0.68–1.46)	1.07 (0.74–1.52)	1.13 (0.79–1.62)	1.17 (0.82–1.64)
	1.00	0.5	0.95 (0.65–1.37)	0.98 (0.67–1.43)	1.09 (0.76–1.57)	1.12 (0.79–1.59)	1.19 (0.84–1.67)
	1.00	1.0	0.85 (0.57–1.25)	0.90 (0.60–1.32)	1.02 (0.70–1.48)	1.07 (0.74–1.54)	1.15 (0.80–1.64)
	1.00	1.5	0.72 (0.46–1.10)	0.76 (0.49–1.14)	0.91 (0.62–1.34)	0.97 (0.66–1.40)	1.09 (0.76–1.58)
	1.00	2.0	0.55 (0.33–0.87)	0.59 (0.37–0.91)	0.77 (0.50–1.15)	0.87 (0.57–1.27)	1.03 (0.71–1.50)
	1.52	0.0	1.52 (1.07–2.18)	1.48 (1.03–2.14)	1.52 (1.07–2.16)	1.52 (1.09–2.15)	1.49 (1.07–2.06)
	1.52	0.5	1.51 (1.05–2.18)	1.50 (1.05–2.17)	1.50 (1.06–2.13)	1.50 (1.05–2.13)	1.50 (1.07–2.11)
	1.52	1.0	1.41 (0.97–2.04)	1.43 (0.98–2.06)	1.43 (0.99–2.03)	1.44 (1.00–2.07)	1.49 (1.07–2.12)
	1.52	1.5	1.24 (0.84–1.83)	1.24 (0.83–1.81)	1.31 (0.91–1.91)	1.38 (0.95–2.03)	1.43 (1.01–2.04)
	1.52	2.0	1.02 (0.67–1.53)	1.03 (0.67–1.51)	1.12 (0.76–1.66)	1.24 (0.84–1.83)	1.34 (0.93–1.93)

Given are medians and 2.5th and 97.5th percentiles in parentheses.
SD, standard deviation.

1.5 in the scenarios with non-differential random recall errors.

Systematic recall errors. The simulated OR for regular use increased with increasing systematic recall errors of cases and decreased with increasing systematic recall errors of controls (Table 3). The same pattern was found for the OR for heavy use of mobile phones. We observed overestimated ORs for regular and heavy use whenever cases had higher systematic recall errors than controls. The opposite occurred when the controls' systematic recall errors were higher than those of cases. These findings were true for both a true OR of 1 and 1.5. Whenever cases and controls had the same amount of systematic recall errors, we observed no biased risk estimates for regular and heavy use of phones, independently of the true OR.

Combined recall errors. When we combined random and systematic recall errors, we observed superposed effects of both types of errors (Table 4). Interestingly, the biased effects of systematic recall errors were shifted towards unity with increasing random recall errors. For example, when assuming no true risk of mobile phones we observed an OR for heavy use of 2.93 when cases overestimated their use by 100% and controls underestimated their use by −50%, both without random error (SD = 0, Table 3). In the corresponding scenario, with the same level of systematic recall errors but considerable random recall errors (SD = 2), an OR of 2.06 was observed for the heavy users (Table 4). The finding that the effects of systematic recall errors were attenuated by the random recall errors were independent of the true assumed risk of mobile phones.

Selection Bias

Our analysis of the non-responder interviews yielded similar participation probabilities for mobile phone users and nonusers among cases (82% and 85%, respectively) and controls (70% and 72%, respectively).

The simulated OR for regular and heavy use of mobile phones underestimated the true risk estimate in the scenarios in which unexposed controls (nonusers of mobile phones) or exposed cases (mobile phone users) were under-represented (Table 5). The opposite was true when unexposed cases were under-represented. For example, when the users among controls had a probability to participate of 0.80 and the nonusers a probability of 0.70, and the users and nonusers among cases had a probability of 0.75, the OR for heavy use dropped from 1.00 to 0.88 when we assumed no risk of mobile phones and from 1.52 to 1.36 when we assumed an association of mobile phone use and brain tumors.

Plausible scenarios for CEFALO

We found almost no bias in the OR for regular use in all three plausible scenarios (Table 6). However, we observed downward biased ORs for heavy use in all three scenarios when a true risk of mobile phones was assumed. When we assumed no recall bias, the extent of risk underestimation was moderate: the OR for heavy use dropped from 1.52 to 1.35 without selection bias and to 1.33 with selection bias. When we assumed that cases overestimate their mobile phone use by 9% and controls by 34%, as observed, the underestimation of the risk was considerable (OR for heavy use of 1.11 instead of 1.52).

DISCUSSION

In this study, we assessed the impact of random and systematic recall error and of selection bias on the ORs for brain tumors in relationship with regular and heavy use of mobile phones. The impact of random recall error was complex. For instance, differential random recall error can result in biased risk estimates even if there is no differential systematic under- or overestimation of exposure between cases and controls. Thus, in terms of bias, differential random recall error is as much important as differential systematic recall error.

Strengths and Limitations

We used objective network operator data about mobile phone use and interviews in non-participants to define our simulations. Thus, the simulations reflect the real situation of the CEFALO case–control study about mobile phone use and brain tumors among children and adolescents. As we simulated a broad range of possible scenarios that may occur in any kind of case–control study, our results are valuable for the interpretation of other case–control studies, in particular, case–control studies of mobile phone use in adults.

Our findings for the most plausible scenarios should, however, be considered as indications since the assumptions about the recall error and selection bias models are subject to uncertainty. Network operator data covering the time period before the diagnosis could only be obtained for a minority of the CEFALO study participants (13.6% of cases and 13.3% of controls). In Switzerland, for example, we only got usable data for the exposure period closest to the actual data collection because all connection data of mobile phone use are deleted 6 months after recording. As a consequence, only data covering the period after the diagnosis date were available for Switzerland, which could not be used for this simulation. In addition,

TABLE 3. Effects of Systematic Recall Errors on the Odds Ratio (OR) for Regular Use and Heavy Use

	Unbiased OR	% Controls	% Under/overestimation cases					
			−50%	−10%	0%	+10%	+50%	+100%
Regular use	1.00	−50	1.00 (0.78–1.31)	1.16 (0.90–1.53)	1.18 (0.91–1.53)	1.20 (0.93–1.58)	1.25 (0.96–1.64)	1.28 (1.00–1.67)
	1.00	−10	0.78 (0.60–1.00)	1.00 (0.77–1.29)	1.03 (0.80–1.35)	1.06 (0.82–1.38)	1.14 (0.88–1.49)	1.20 (0.94–1.57)
	1.00	0	0.75 (0.58–0.97)	0.97 (0.75–1.25)	1.00 (0.78–1.31)	1.03 (0.80–1.35)	1.12 (0.87–1.46)	1.18 (0.92–1.55)
	1.00	+10	0.71 (0.54–0.93)	0.94 (0.73–1.21)	0.97 (0.75–1.26)	1.00 (0.77–1.31)	1.09 (0.85–1.42)	1.16 (0.90–1.52)
	1.00	+50	0.59 (0.46–0.77)	0.82 (0.63–1.05)	0.86 (0.66–1.11)	0.90 (0.69–1.17)	1.00 (0.78–1.30)	1.09 (0.85–1.42)
	1.00	+100	0.47 (0.36–0.61)	0.71 (0.55–0.91)	0.75 (0.58–0.97)	0.78 (0.60–1.01)	0.90 (0.70–1.16)	1.00 (0.78–1.30)
	1.17	−50	1.17 (0.91–1.54)	1.35 (1.05–1.77)	1.38 (1.07–1.82)	1.41 (1.08–1.85)	1.44 (1.10–1.88)	1.46 (1.13–1.94)
	1.17	−10	0.93 (0.72–1.21)	1.18 (0.91–1.54)	1.22 (0.94–1.60)	1.25 (0.95–1.62)	1.33 (1.02–1.75)	1.41 (1.08–1.84)
	1.17	0	0.90 (0.69–1.16)	1.14 (0.88–1.49)	1.18 (0.91–1.54)	1.21 (0.93–1.58)	1.31 (1.00–1.72)	1.38 (1.07–1.81)
	1.17	+10	0.85 (0.64–1.09)	1.10 (0.85–1.44)	1.14 (0.88–1.48)	1.17 (0.90–1.53)	1.28 (0.98–1.69)	1.36 (1.05–1.78)
	1.17	+50	0.72 (0.55–0.94)	0.97 (0.75–1.27)	1.01 (0.78–1.32)	1.05 (0.80–1.36)	1.17 (0.90–1.55)	1.28 (0.99–1.68)
	1.17	+100	0.59 (0.46–0.77)	0.85 (0.65–1.10)	0.90 (0.69–1.16)	0.93 (0.71–1.20)	1.05 (0.81–1.37)	1.18 (0.91–1.54)
Heavy use	1.00	−50	0.98 (0.66–1.44)	1.75 (1.24–2.50)	1.88 (1.34–2.66)	2.02 (1.44–2.86)	2.48 (1.78–3.47)	2.93 (2.12–4.09)
	1.00	−10	0.47 (0.29–0.72)	0.99 (0.67–1.43)	1.10 (0.75–1.61)	1.23 (0.85–1.77)	1.62 (1.14–2.29)	2.02 (1.45–2.85)
	1.00	0	0.41 (0.25–0.65)	0.88 (0.59–1.28)	0.99 (0.67–1.46)	1.11 (0.75–1.59)	1.50 (1.04–2.12)	1.89 (1.35–2.66)
	1.00	+10	0.36 (0.21–0.55)	0.78 (0.52–1.16)	0.88 (0.59–1.31)	0.99 (0.66–1.43)	1.36 (0.95–1.93)	1.75 (1.25–2.49)
	1.00	+50	0.23 (0.12–0.37)	0.54 (0.35–0.82)	0.62 (0.40–0.95)	0.69 (0.45–1.04)	0.99 (0.67–1.43)	1.35 (0.94–1.94)
	1.00	+100	0.13 (0.06–0.23)	0.35 (0.21–0.55)	0.41 (0.25–0.65)	0.47 (0.29–0.72)	0.69 (0.45–1.02)	0.98 (0.67–1.43)
	1.52	−50	1.51 (1.06–2.16)	2.41 (1.73–3.40)	2.61 (1.86–3.66)	2.77 (2.00–3.90)	3.26 (2.35–4.53)	3.66 (2.65–5.19)
	1.52	−10	0.83 (0.55–1.22)	1.53 (1.06–2.18)	1.66 (1.16–2.37)	1.80 (1.27–2.54)	2.26 (1.61–3.21)	2.77 (2.00–3.89)
	1.52	0	0.74 (0.49–1.10)	1.39 (0.97–2.00)	1.53 (1.06–2.19)	1.65 (1.17–2.33)	2.11 (1.50–3.01)	2.60 (1.87–3.65)
	1.52	+10	0.66 (0.43–0.97)	1.27 (0.88–1.83)	1.39 (0.96–2.00)	1.53 (1.07–2.17)	1.96 (1.39–2.79)	2.42 (1.74–3.42)
	1.52	+50	0.41 (0.25–0.64)	0.92 (0.62–1.34)	1.03 (0.71–1.50)	1.14 (0.79–1.65)	1.52 (1.06–2.19)	1.97 (1.40–2.80)
	1.52	+100	0.25 (0.14–0.40)	0.65 (0.43–0.97)	0.74 (0.49–1.10)	0.83 (0.55–1.21)	1.14 (0.78–1.65)	1.53 (1.08–2.19)

Given are medians and 2.5th and 97.5th percentiles in parentheses.

TABLE 4. Effects of Combinations of Random and Systematic Recall Errors on the Odds Ratio (OR) for Regular and Heavy Use of Mobile Phones

				Cases			
	Unbiased OR	% Under/ overestimation	SD	−50%	+100%	−50%	+100%
				1	1	2	2
Regular use	1.00	−50	1	1.00 (0.77–1.31)	1.25 (0.96–1.62)	0.81 (0.63–1.04)	1.10 (0.85–1.43)
	1.00	+100	1	0.57 (0.44–0.74)	1.01 (0.78–1.31)	0.49 (0.37–0.63)	0.82 (0.63–1.05)
	1.00	−50	2	1.19 (0.91–1.55)	1.30 (1.00–1.70)	1.01 (0.78–1.30)	1.21 (0.94–1.58)
	1.00	+100	2	0.87 (0.67–1.13)	1.20 (0.93–1.57)	0.69 (0.54–0.90)	1.02 (0.79–1.32)
	1.17	−50	1	1.17 (0.89–1.53)	1.44 (1.10–1.88)	1.37 (1.04–1.80)	1.49 (1.14–1.96)
	1.17	+100	1	0.70 (0.53–0.89)	1.17 (0.90–1.52)	1.03 (0.79–1.34)	1.38 (1.05–1.79)
	1.17	−50	2	0.94 (0.72–1.21)	1.24 (0.96–1.63)	1.17 (0.90–1.52)	1.38 (1.07–1.84)
	1.17	+100	2	0.57 (0.44–0.74)	0.95 (0.74–1.24)	0.82 (0.63–1.05)	1.15 (0.90–1.52)
Heavy use	1.00	−50	1	1.00 (0.69–1.47)	2.56 (1.87–3.54)	1.11 (0.77–1.56)	2.27 (1.65–3.15)
	1.00	+100	1	0.20 (0.10–0.33)	1.02 (0.70–1.48)	0.40 (0.25–0.61)	1.12 (0.78–1.58)
	1.00	−50	2	0.74 (0.48–1.12)	2.15 (1.54–3.03)	0.99 (0.67–1.43)	2.06 (1.46–2.87)
	1.00	+100	2	0.14 (0.06–0.26)	0.76 (0.49–1.15)	0.33 (0.20–0.53)	0.98 (0.66–1.43)
	1.52	−50	1	1.44 (1.00–2.09)	3.25 (2.34–4.53)	1.13 (0.75–1.68)	2.79 (1.99–3.90)
	1.52	+100	1	0.33 (0.20–0.53)	1.44 (0.99–2.05)	0.23 (0.11–0.40)	1.15 (0.78–1.67)
	1.52	−50	2	1.41 (0.98–1.99)	2.75 (2.00–3.87)	1.31 (0.90–1.87)	2.56 (1.84–3.62)
	1.52	+100	2	0.55 (0.36–0.81)	1.43 (1.01–2.02)	0.49 (0.30–0.74)	1.28 (0.88–1.85)

Given are medians and 2.5th and 97.5th percentiles in parentheses.
SD, standard deviation.

attribution of network operator data to the user is subject to uncertainty in children and adolescents because network operator data could only be requested if the participants were able to recollect their subscription and corresponding phone number. In Sweden, the network operators also used the ID number of the study participant to identify the mobile phone records. However, subscriptions were sometimes held by the parents and a

TABLE 5. Effects of Selection Bias on the Odds Ratio (OR) for Regular and Heavy Use of Mobile Phones

Participation probabilities							
Cases		Controls		Regular use		Heavy use	
User	Nonuser	User	Nonuser	Unbiased OR	Simulated OR	Unbiased OR	Simulated OR
No selection bias							
1	1	1	1	1.00	1.00 (0.78–1.31)	1.00	0.98 (0.66–1.44)
1	1	1	1	1.17	1.17 (0.91–1.54)	1.52	1.52 (1.06–2.17)
Overselection of exposed controls							
0.75	0.75	0.80	0.70	1.00	0.89 (0.67–1.22)	1.00	0.88 (0.56–1.36)
0.75	0.75	0.80	0.70	1.17	1.05 (0.78–1.43)	1.52	1.36 (0.89–2.06)
Overselection of exposed cases							
0.80	0.70	0.75	0.75	1.00	1.12 (0.83–1.52)	1.00	1.10 (0.71–1.69)
0.80	0.70	0.75	0.75	1.17	1.31 (0.98–1.79)	1.52	1.70 (1.12–2.56)
Overselection of exposed controls with low participation rate of controls							
0.75	0.75	0.60	0.40	1.00	0.72 (0.52–1.00)	1.00	0.70 (0.44–1.12)
0.75	0.75	0.60	0.40	1.17	0.84 (0.60–1.17)	1.52	1.09 (0.69–1.68)
Overselection of exposed cases with low participation rate of controls							
0.80	0.70	0.50	0.50	1.00	1.12 (0.81–1.55)	1.00	1.10 (0.68–1.76)
0.80	0.70	0.50	0.50	1.17	1.31 (0.95–1.82)	1.52	1.70 (1.08–2.66)
Overselection of exposed cases and controls with low participation rate of controls							
0.80	0.70	0.60	0.40	1.00	0.80 (0.58–1.12)	1.00	0.78 (0.50–1.25)
0.80	0.70	0.60	0.40	1.17	0.94 (0.67–1.32)	1.52	1.22 (0.78–1.88)

Given are medians and 2.5th and 97.5th percentiles in parentheses.

TABLE 6. Impact of the Plausible Scenarios for CEFALO

Ratio recalled/operator		SD of ratio		Participation probabilities				Regular use		Heavy use	
				Cases		Controls					
Cases	Controls	Cases	Controls	User	Nonuser	User	Nonuser	Unbiased OR	Simulated OR	Unbiased OR	Simulated OR
No recall bias, no selection bias											
1.23 (0.53–3.75)	1.23 (0.53–3.75)	1.62	1.62	0.83	0.83	0.71	0.71	1.00	1.01 (0.75–1.35)	1.00	0.98 (0.62–1.50)
								1.17	1.17 (0.88–1.58)	1.52	1.35 (0.88–2.03)
No recall bias but selection bias											
1.23 (0.53–3.75)	1.23 (0.53–3.75)	1.62	1.62	0.82	0.85	0.70	0.72	1.00	0.99 (0.74–1.34)	1.00	0.97 (0.62–1.49)
								1.17	1.17 (0.86–1.56)	1.52	1.33 (0.88–2.00)
Differential systematic and random recall bias and selection bias											
1.09 (0.47–2.27)	1.34 (0.63–5.36)	1.41	1.70	0.82	0.85	0.70	0.72	1.00	1.01 (0.75–1.36)	1.00	0.77 (0.48–1.20)
								1.17	1.19 (0.88–1.59)	1.52	1.11 (0.73–1.71)

Given are medians and 2.5th and 97.5th percentiles in parentheses.
SD, standard deviation.

considerable effort was required to correctly identify the actual user of the mobile phone. To assess the representativeness of the participants with operator data, we compared these subjects with the study participants from Denmark and Sweden in CEFALO for whom no operator data were provided. We found no evidence for a difference between the participants for whom operator data were available and those with no operator data in terms of cumulative duration and number of calls; cases with no operator data had a median cumulative duration of calls of 1,747 min while those with operator data had a median of 1,402 min (Mann–Whitney *U*-test, $P = 0.98$). Controls with no operator data had a median cumulative duration of calls of 1,700 min while those with operator data had a median of 2,797 min (Mann–Whitney *U*-test, $P = 0.51$). Cases with no operator data had a median cumulative number of calls of 929 and cases with operator data had a median of 1,104 min (Mann–Whitney *U*-test, $P = 0.43$). Controls with no operator data had a median cumulative duration of calls of 840 min and controls with operator data had a median of 1,380 min (Mann–Whitney *U*-test, $P = 0.58$). Furthermore, neither sex distribution (cases: Chi-square test, $P = 0.40$; controls: $P = 0.28$), nor age distribution (cases: $P = 0.99$; controls: $P = 0.75$) was different between these two collectives. In addition, our simulations were simplified. We did not consider potential latency effects or possible confounding factors in our simulations, or the age-dependency of mobile phone use, but we did not expect these simplifications to change the general pattern.

Comparison of Self-Reported and Operator-Recorded Mobile Phone Use

In our study, we found that number of calls as well as duration of mobile phone use was overestimated by cases as well as controls. Whereas overestimation of duration of calls was observed in adults as well, numbers of calls were mainly underestimated in previous validation studies of adults and in an Australian study of adolescents [Inyang et al., 2009; Vrijheid et al., 2009a].

An unexpected result of our validation is that controls appeared to overestimate their use more than cases. While the difference between cases and controls was not statistically significant for number of calls, we found borderline significant evidence for a difference for duration of calls. In fact, the opposite pattern is more often observed in epidemiology; cases tend to retrospectively overestimate their exposure, probably because they seek an explanation for their disease and thus are expected to reflect more intensely about past exposure [Drews and Greeland, 1990; Infante-Rivard and Jacques, 2000]. There was some evidence in the INTERPHONE study that the recall error increased with increasing time before interview in cases whereas no such trend was seen among controls [Vrijheid et al., 2009a]. However, confidence intervals were wide in our study and it is doubtful if the amount of overestimation really differs between cases and controls. However, if the recall errors are differential, this could lead to underestimation of the risk in the highest exposure category if mobile phones are a risk factor for brain tumors. In the CEFALO study we found little indication that the amount of overestimation is larger in cases than in controls. For this reason we also defined two plausible scenarios with the amount of overestimation being the same for cases and controls. Furthermore, the nature of the self-reported and operator-recorded mobile phone use data differed. While the participants of the CEFALO study were asked to estimate their mobile phone use in categories, network operators provided continuous data. Because the participants of CEFALO

indicated their amount of mobile phone use on a predefined categorical scale, extreme outliers as observed in the INTERPHONE study could not occur. However, variation of the self-reported data is limited by definition by the response categories, which may result in an underestimation of heavy mobile phone use. Furthermore, participants may have had the tendency to avoid the extreme response categories and choose a category that is not the highest or lowest. These circumstances constitute a limitation of the validation of self-reported mobile phone use and restrict the generalizability of our findings to other studies that used predefined categories of mobile phone use.

In terms of selection bias, our results are also not in line with the INTERPHONE study [Vrijheid et al., 2009b; INTERPHONE Study Group, 2010]. In the INTERPHONE study, the mobile phone users were more likely to participate, whereas our interviews of non-participating controls suggest that in CEFALO there is only a very small difference in participation rate between mobile phone users and nonusers.

Recall Errors

It is well known that bias introduced by random recall error shifts the risk estimate based on a binary exposure toward the null value [Newell, 1962; Keys and Kihlberg, 1963; Gullen et al., 1968; Copeland et al., 1977]. When the exposure has more than two categories (i.e., is polytomous), random recall errors can lead to bias away from unity [Walker and Blettner, 1985; Dosemeci et al., 1990; Birkett, 1992]. We consistently found a complex pattern when we introduced random recall errors in our simulations. Even if cases and controls had no systematic recall errors on average, but cases had a higher variation in their recall errors than controls, the risk estimates for regular use of mobile phones underestimated the true risk while the OR for heavy users was virtually unbiased (Table 2). When we re-ran the simulations but used the 90th percentile of the observed exposure distribution among controls as cut-off for classifying the heavy users, higher random recall errors among cases than controls led to an increase in the OR for heavy use (data not shown). The reason for this apparently paradox observation is the categorization or dichotomization of the exposure variable. With increasing random errors, the proportion of study participants in the most extreme (i.e., lowest and highest) exposure categories is increasing. Thus, a higher random recall error in cases results in a shift of regular users to non-regular users among cases and at the same time an increase in the number of heavy users among cases. This produces a biased increased risk for heavy users as well as a biased decreased risk of regular users compared to nonusers.

When the true OR was 1.5, the scenarios with non-differential random recall errors (i.e., the diagonal cells in Table 2 with the same amount of random recall errors among cases and controls) showed a decrease in the OR for heavy use but not for regular use. This result is not intuitively understood. One would expect the OR for heavy use to be unbiased when the random recall error is non-differential because the change in the observed distribution of phone use is the same in cases and controls. But one has to note that the cases have a higher phone use on average in the scenarios where we assumed a true risk of mobile phones. Furthermore, the observed 75th percentile of controls—the cut-off to classify the heavy users—increases due to the increased recall variance of controls. Therefore, the proportion of cases which are classified as heavy users decreases with increasing random recall errors of controls and eventually leads to the obtained decrease in the OR for heavy use even when random recall errors were non-differential.

Effects of systematic recall errors on the risk estimates were less complex. Our simulation demonstrates that corresponding to the direction of the systematic recall errors of cases and controls, the observed risk estimates can either exaggerate or underestimate the true risk.

Effects of combined random and systematic recall errors were combinations of both errors. Larger random recall error in combination with systematic error led to shifts of ORs toward unity compared to scenarios with systematic recall error only.

Selection Bias

In theory, the impact of selection bias can be estimated by the ratio of the participation probabilities of exposed and unexposed among cases and controls [for calculation, see Vrijheid et al., 2006; Rothman et al., 2008]. The results of our simulation incorporating selection bias are in line with those predictions. Our simulations suggest that reasonable values of selection bias could lead to substantially biased risk estimates as hypothesized for the INTERPHONE [INTERPHONE Study Group, 2010]. However, this is unlikely to occur in CEFALO (see below).

Plausible Scenarios for CEFALO

Our comparison of the self-reported data with the network operator data provided no evidence that cases more strongly overestimate their mobile phone use than controls. Thus, a false positive result is unlikely to occur in CEFALO. However, in the scenario with differential random and systematic recall error, the OR for heavy users was underestimated, independent of the true risk

of phones. Thus, we may miss a potential risk if controls effectively overestimate their use more than cases. Because this is against the general experience from case–control studies dealing with self-reported exposure and as the IQRs of the overestimation are quite wide, it is well possible that the amount of overestimation is the same in cases and controls. In this case, our study yielded robust results with only little underestimation of the true risk for heavy mobile phone users. Most importantly, participation bias, which is of concern in the INTERPHONE study, is unlikely to have a major impact in CEFALO because participation rates were high in cases and controls and analyses of non-responder interviews found only slightly different participation rates for users and non-mobile phone users among controls. Thus, we do not expect to find protective risk estimates in the CEFALO study.

CONCLUSIONS

Our simulation models based on the plausible error scenarios suggest that it is unlikely that error and bias produce a false positive association in the forthcoming analyses of the CEFALO study, both in the direction of a spurious risk and spurious protective effect. The simulations further suggest that errors and bias leading to an underestimation of the strength of the association are so small that if a detectable association exists, and if the overestimation of mobile phone use in controls is not much larger than in cases, it is likely that this association will show up in the risk analyses.

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3.2 Article 2: Predictors and overestimation of recalled mobile phone use among children and adolescents

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Review

Predictors and overestimation of recalled mobile phone use among children and adolescents

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ABSTRACT

A growing body of literature addresses possible health effects of mobile phone use in children and adolescents by relying on the study participants' retrospective reconstruction of mobile phone use. In this study, we used data from the international case–control study CEFALO to compare self-reported with objectively operator-recorded mobile phone use. The aim of the study was to assess predictors of level of mobile phone use as well as factors that are associated with overestimating own mobile phone use. For cumulative number and duration of calls as well as for time since first subscription we calculated the ratio of self-reported to operator-recorded mobile phone use. We used multiple linear regression models to assess possible predictors of the average number and duration of calls per day and logistic regression models to assess possible predictors of overestimation.

The cumulative number and duration of calls as well as the time since first subscription of mobile phones were overestimated on average by the study participants. Likelihood to overestimate number and duration of calls was not significantly different for controls compared to cases (OR = 1.1, 95%-CI: 0.5 to 2.5 and OR = 1.9, 95%-CI: 0.85 to 4.3, respectively). However, likelihood to overestimate was associated with other health related factors such as age and sex. As a consequence, such factors act as confounders in studies relying solely on self-reported mobile phone use and have to be considered in the analysis.

Contents

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1. Introduction

Mobile phones experienced a dramatic increase in popularity and ownership since the 1990s among adults (Schüz, 2005). Already in 2002, the use of mobile phones was common among children and adolescents: In a systematic study involving 1933 primary school children in Germany, 34.7% reported owning a mobile phone (Böhler and Schüz, 2004). In Sweden, as much as 91% of 15 to 19 years olds reported owning a mobile phone already in 2001 (Schüz, 2005).

This increase in mobile phone ownership and presumably in mobile phone use has generated anxiety of possible adverse health effects associated with exposure to radiofrequency electromagnetic fields (RF EMF) emitted by such devices. Because the handset is held in close proximity to the head resulting in exposure of the brain, tumours of the brain have been of primary concern. Furthermore, it has been argued that children may be more susceptible to RF EMF due to their still developing nervous system (Kheifets et al., 2005).

Only few studies have addressed the possible relationship between exposure to RF EMF and health outcomes in children and adolescents (Divan et al., 2008; Haarala et al., 2005; Hardell and Carlberg, 2009; Koivusilta et al., 2005; Krause et al., 2006; Kwon et al., 2010; Preece et al., 2005; Punamaki et al., 2007; Sanchez-Martinez and Otero, 2009; Thomas et al., 2010; Van den Bulck, 2007). Many of these studies used self-reported mobile phone use as exposure while some of them used objective exposure data. In summary, there seems to be a systematic difference between the studies using self-reported exposure data and the studies using objective exposure data, for instance in a double blind laboratory experiment. The latter are less likely to report effects. One explanation could be that such studies capture only short term exposure effects. Nevertheless, results from studies that used self-reported mobile phone use must be interpreted with caution as the accuracy of recall among children and adolescents has been demonstrated being rather poor (Aydin et al., 2011a; Inyang et al., 2009). So far it is not clear whether poor estimation of own mobile phone use is associated with specific health-related characteristics of the study participants. Knowledge of factors that are associated with overestimation of mobile phone use could be useful for the interpretation of previous studies that used self-reported data for exposure assessment.

In this report, we assessed possible predictors of level mobile phone use and explored factors that are related to overestimation of mobile phone use using data from a recent case-control study on brain tumours in children and adolescents carried out in Denmark, Norway, Sweden, and Switzerland (CEFALO study). In particular, we used objective operator-recorded data from Denmark, Sweden and Switzerland to compare self-reported with operator-recorded amount of mobile phone use.

2. Subjects and methods

In 2006, CEFALO, an international case-control study of the association between the use of mobile phones and the risk of brain tumours among children aged 7–19 years was set up in Denmark, Norway, Sweden, and Switzerland. Eligible cases were all children of age 7–19 years diagnosed during the study period (2004–2008) with intracranial central nervous system tumours (CNS). Two controls were randomly selected from a population-based registry of the total population of the study area, matched on age, sex, and residential area. The reference date for exposure assessment was the date of diagnosis for cases and the date of diagnosis of the matched case for controls.

Past mobile phone use was assessed with a detailed questionnaire during face-to-face interviews with the participants and their parents. The participants stated the amount of mobile phone use on pre-defined categorical scales. For number of calls, there were 6 pre-defined categories ranging from <1/week to ≥ 5/day and for duration of calls there were 4 categories ranging from ≤ 1 to ≥ 10 min/call. The participants also had to give information about the length of the corresponding usage period in months. The amount of mobile phone use and the duration of the usage period were then used to calculate the cumulative number and duration of calls for each participant. We used the midpoint of the categories to calculate continuous exposure measures (e.g. we used 1.5 calls/week if a participant checked the category 1–2 calls/week). If a participant checked the lowest or the highest category that did not have a midpoint, we used 2 calls/month or 7 calls/day for number of calls and 1 min or 15 min for duration of calls, respectively.

Study participants were asked to give consent to allow the researchers to get access to traffic data from mobile phone network operators. Data were provided by two network operators in Sweden, three in Denmark and three in Switzerland. Operators were asked for data linked to a specific personal identification number, phone number or name or a combination of any of the data given by the study participants. From the network operators, we received information about number of calls, duration of calls as well as subscription start and end dates. In Switzerland, traffic data is deleted after six months. Thus, only data covering the period after the reference date were available in Switzerland. As a consequence, only time since first use of phones could be used from the operator-recorded data from Switzerland. Periods of reported mobile phone use were matched to operator-recorded periods for each subject. If the overlap between self-reported subscription periods and operator-recorded subscription periods were incomplete, only the cumulative number and duration of calls that occurred during the overlapping period were used. For the self-reported cumulative number and duration of calls as well as the time since first use of mobile phones the ratio of self-reported to operator-recorded mobile phone use was calculated. Ratios > 1 denote overestimation while ratios < 1 correspond to underestimation of mobile phone use. We present the median ratio and the corresponding interquartile range (IQR). In addition, we calculated Spearman's correlation coefficients between log-transformed self-reported cumulative number and duration of calls as well as time since first use of mobile phones. First, we included only those participants with available self-reported and operator-recorded data. Second, we included those participants who stated never using mobile phones and set their self-reported and operator-recorded number and duration of calls to zero.

Further, we used multiple linear regression models to assess possible predictors of the operator recorded amount of mobile phone use. Log-transformed average number and duration of calls per day served as dependent variables while explanatory variables were country, gender, age (continuous), SES of parents based on their education (low, intermediate, high) and if the subject had any older siblings (yes, no). Here, we present the antilog back transformed coefficients with their corresponding 95%-confidence intervals (95%-CIs).

In a second analysis, we created a binary variable indicating overestimation based on the ratio of recalled to operator-recorded phone use: for subjects with a ratio ≥ 1.5 the binary variable was coded 1 and for subjects with a ratio < 1.5 it was coded 0. We then used a logistic regression model to assess possible predictors of overestimation. We considered the following variables as possible predictors of overestimation of mobile phone use: country, health status (case, control), age (7–14, 15–19 years), gender, socio-economic status of the parents (low, intermediate, high), time between reference date and interview (<1.5 years, ≥ 1.5 years) and amount of operator-recorded phone use (tertiles served as cut-offs). Here, we present odds ratios (ORs) and 95%-CIs of the logistic regression models. First, we included each possible predictor variable

separately to calculate crude odds ratios. Second, we included all variables concurrently in a model to obtain adjusted odds ratios. As a sensitivity analysis, we also calculated models to assess possible factors related to underestimation (ratio ≤ 0.5).

The software Stata/SE (version 10.1) was used for all analyses (StataCorp, 2007).

3. Results

Characteristics of the study participants are shown in Table 1. Operator data about number and duration of calls were obtained from 48 cases and 87 control subjects (Table 1). This corresponds to 31% and 32% of the Danish and Swedish study participants who reported owning a mobile phone. In addition, information about time since first subscription was available from 36 Swiss cases (80%) and 65 Swiss controls (76%).

The cumulative number of calls were slightly overestimated on average by both cases (median ratio = 1.09, IQR = 0.47–2.27) and controls (median ratio = 1.34 [0.63–5.36]) (Fig. 1A). The Spearman's correlation coefficient for number of calls was 0.57 (95%-CI: 0.44–0.67) and 0.93 (95% CI: 0.91–0.94) when we included those participants who stated never using a mobile phone. The same pattern but somewhat higher ratios was found for cumulative duration of calls for cases (median ratio = 1.52 [0.70–4.28]) and for controls (median ratio = 2.63 [0.89–10.06]) (Fig. 1B). The Spearman's correlation coefficient for duration of calls was 0.57 (95%-CI: 0.46–0.68) and 0.93 (95% CI: 0.92–0.94) when we included those participants who stated never using a mobile phone. For the time since first subscription the respective median ratios and IQRs were 1.25 (0.98–2.40) for cases and 1.28 (0.98–2.37) for controls (Fig. 1C). The Spearman's correlation coefficient for time since first use of mobile phones was 0.41 (95%-CI: 0.30–0.51) and 0.94 (95% CI: 0.93–0.95) when we included those participants who stated never using a mobile phone. Controls showed a tendency of overestimating more than cases, but the variation was very large and the difference was not statistically significant.

Participants from Sweden had significantly less average number of calls per day (−61%) compared to participants from Denmark (Table 2). All other factors were not found to be significantly related with frequency and amount of mobile phone use per day. Male participants tended to have a lower average number and duration of calls per day than female participants. Per year of age, average numbers and duration of calls per day increased by 7%, although not statistically significant. Children with one or more parents with the highest socio-economic status (SES) based on their educational level tended to have lower average number and duration of calls per day compared to children with parents of the lowest SES. Children who had at least one older sibling showed a tendency towards a higher average number and duration of calls per day compared to children with no older siblings.

In the multiple logistic regression model, participants of CEFALO aged 15–19 had a significantly higher likelihood of overestimating their cumulative number and duration of calls compared to participants aged 7–14 (Table 3). Female participants were more likely to overestimate duration of calls than male participants. A higher amount of operator recorded mobile phone use was associated with a lower probability of overestimating the mobile phone use. The other factors were not significantly related to overestimation. Notably, cases did not overestimate their mobile phone use more often than controls, rather the opposite. Time between interview and reference date was not associated with the likelihood of overestimating the use of mobile phone.

In the sensitivity analysis we assessed the possible factors related to underestimation (ratio ≤ 0.5) the majority of the ORs were close to the inverse of the ORs in the models for overestimation.

Table 1
Characteristics of study participants.

	Cases		Controls	
	N	%	N	%
Total CEFALO participants	352	–	646	–
Operator and self-reported data available	48	100.0	87	100.0
Gender				
Male	20	41.7	39	44.8
Female	28	58.3	48	55.2
Country[a]				
Denmark	20	41.7	29	33.3
Sweden	28	58.3	58	66.6
Age				
7–14	24	50.0	46	52.9
15–19	24	50.0	41	47.1
SES of parents (education)				
Low	5	10.4	7	8.0
Intermediate	29	60.4	40	46.0
High	14	29.2	40	46.0
SES of parents (job)				
Low	9	18.7	17	19.5
Intermediate	25	52.1	41	47.1
High	14	29.2	29	33.3
Any older siblings?				
No	25	52.1	42	48.3
Yes	23	47.9	45	51.7

[a] 36 case patients and 65 control participants from Switzerland with operator-recorded start of subscription. These data, however, were only used for the comparison with self-reported start of mobile phone use and were not included in the models.

4.1. Strengths and limitations

To our knowledge, this is one of the first studies assessing possible predictors of overestimation of self-reported mobile phone use among children and adolescents using objective operator-recorded data. We used objective data from network operators to validate the self-reported mobile phone use and to assess possible predictors of overestimation of mobile phone use. One of the limitations of the study is the fact that operator-recorded

Table 2
Predictors affecting level of mobile telephone use per day. Given are exponentiated regression coefficients and their corresponding 95%-CI.

Variable	Number of calls	Duration of calls
	Coefficients (95%-CI)	Coefficients (95%-CI)
Country		
Denmark	1.0	1.0
Sweden	0.39 (0.21–0.74)	0.65 (0.35–1.20)
Gender		
Female	1.0	1.0
Male	0.89 (0.50–1.60)	0.87 (0.49–1.55)
Age (per 1 year)	1.07 (0.95–1.22)	1.07 (0.94–1.21)
SES-education[a]		
Low	1.0	1.0
Intermediate	1.15 (0.39–3.38)	0.68 (0.23–1.99)
High	0.83 (0.28–2.49)	0.52 (0.18–1.53)
Any older siblings?		
No	1.0	1.0
Yes	1.60 (0.90–2.85)	1.42 (0.81–2.51)

[a] Low: elementary school not completed; intermediate: elementary school, high school or apprenticeship; high: university or technical college.

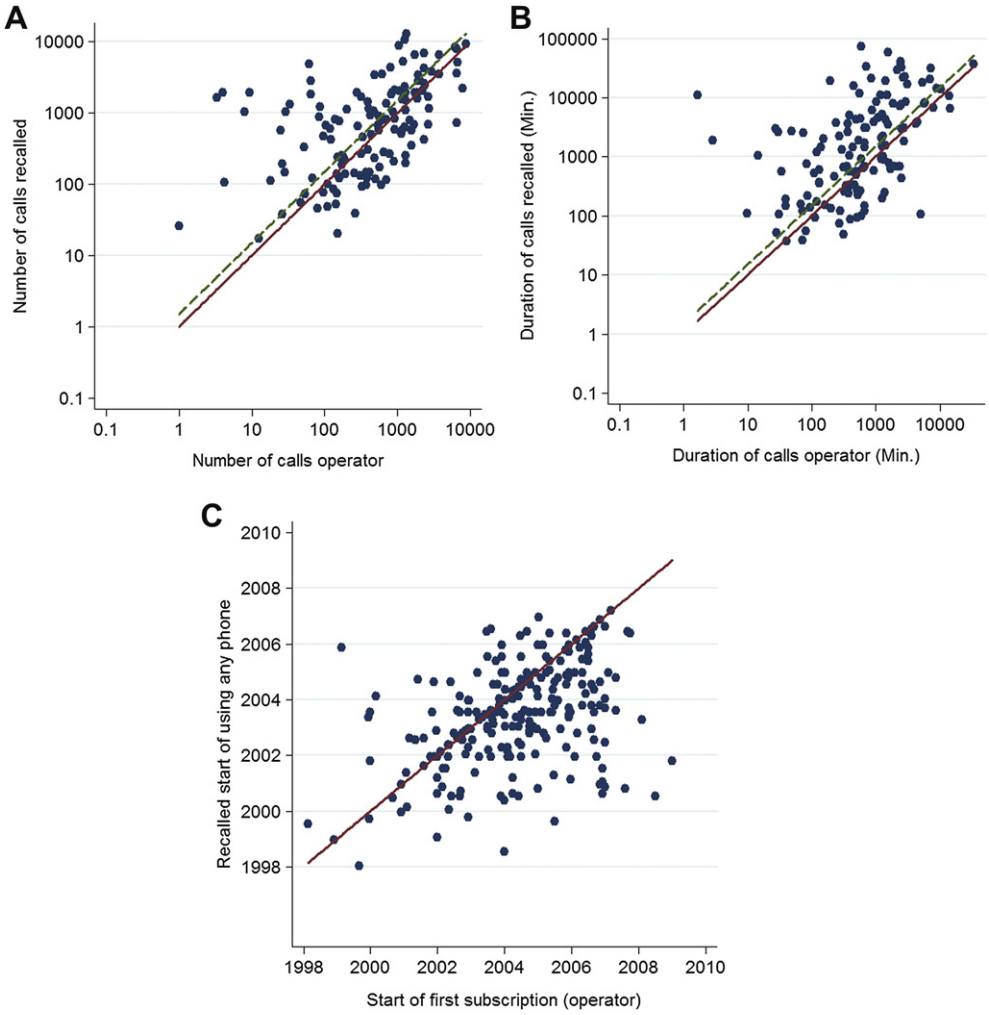

Fig. 1. Scatterplot of (A) number of calls, (B) duration of calls (in minutes) and (C) time since first use of mobile phones self-reported against the operator recorded use. The solid line denotes the line of equality and the dashed line denotes a ratio of recalled to operator-recorded amount of use $\geq$1.5.

data about frequency and amount of mobile phone use were only available for a minority of CEFALO participants (for 32% of the Danish and Swedish study participants who owned a mobile phone). The sample size was small. In combination with large data variability, estimated regression coefficients were imprecise, as reflected by wide 95% confidence intervals. Furthermore, the link between operator-recorded data and user is subject to uncertainty because the participants had to recollect their subscription and corresponding phone numbers. In addition, subscriptions were sometimes held in the name of the parents (Aydin et al., 2011b). As a result considerable discrepancies between self-reported and operator recorded start of first subscription in Fig. 1C may not only be due to poor recollection but also due to imperfect operator data. For instance, reporting to have started mobile phone use recently (e.g. 2006) and having a subscription since 1999 may point towards an inherited subscription from the parents. In contrast, reporting an early start of mobile phone use (e.g. before 2002) with a late recorded subscription (e.g. after 2006) may indicate a subscription change and a missing previous subscription (e.g. due to technical reasons or lack of phone number). Thus, we conclude that retrospectively collected operator data are a limited gold standard.

We found no strong predictors of level of mobile phone use and could not replicate the findings of Inyang et al. (2010) who found that parental socio-economic status was associated with the level of mobile phone use. One would expect an increase of mobile phone use with age. This trend was relatively weak in our data and did not reach statistical significance. This result is most likely explained by the fact that we considered average mobile phone use for each study participant during all subscription periods and not only the current mobile phone use. Thus, increasing use with age is expected to be diluted with rare use during early subscriptions.

Our findings indicate that children and adolescents tend to overestimate both the cumulative number of calls and duration of calls. Virtually all studies that validated self-reported phone use with operator-recorded data in adults or children found that the cumulative duration of calls was overestimated (Tokola et al., 2008; Vrijheid et al., 2009, 2006a). The pattern of recall of cumulative number of calls is less clear. The majority of studies in adults found an underestimation of cumulative number of calls (Vrijheid et al., 2009, 2006a). Among children and adolescents, only one other study compared self-reported with operator recorded data. Based on a relatively low number of participants the study found that cumulative number of calls was overestimated by low-users and underestimated by heavy-users (Inyang et al., 2009) as was observed in our study. Another study comparing self-reported with operator-recorded text messages (SMS) in adolescents found that low users tended to overestimate their number of SMS while heavy users tended to underestimation (Redmayne et al., 2011). However,

Table 3
Predictors of overestimation of mobile phone use.[a] Given are crude odds ratios (cOR), adjusted[b] odds ratios (aORs) and the corresponding 95%-CI.

Variable	Number of calls				Duration of calls			
	Overest. No.	Other No.	cOR (95%-CI)	aOR (95%-CI)	Overest. No.	Other No.	cOR (95%-CI)	aOR (95%-CI)
Country								
Denmark	13	36	1.0	1.0	31	18	1.0	1.0
Sweden	41	44	2.58 (1.20–5.54)	1.71 (0.71–4.14)	46	39	0.68 (0.33–1.41)	0.52 (0.21–1.26)
Health status								
Case	17	31	1.0	1.0	24	24	1.0	1.0
Control	37	49	1.38 (0.66–2.86)	1.10 (0.50–2.45)	53	33	1.61 (0.79–3.28)	1.90 (0.85–4.27)
Age group								
7–14	24	46	1.0	1.0	33	36	1.0	1.0
15–19	30	34	1.69 (0.84–3.39)	2.30 (1.00–5.29)	44	21	2.29 (1.13–4.61)	3.22 (1.40–7.40)
Gender								
Male	22	37	1.0	1.0	28	30	1.0	1.0
Female	32	43	1.25 (0.62–2.52)	1.08 (0.49–2.35)	49	27	1.94 (0.97–3.90)	2.76 (1.22–6.24)
SES of parents (education)[c]								
Low	14	12	1.0	1.0	15	10	1.0	1.0
Intermediate	43	23	0.51 (0.15–1.76)	0.61 (0.15–2.51)	39	27	1.08 (0.31–3.77)	1.38 (0.32–5.99)
High	23	19	0.86 (0.25–3.01)	0.95 (0.23–3.96)	23	20	0.83 (0.23–2.94)	1.02 (0.23–4.54)
Time between reference and interview date								
<1.5 years	52	36	1.0	1.0	44	44	1.0	1.0
≥1.5 years	28	18	0.93 (0.45–1.92)	0.76 (0.31–1.83)	33	13	2.54 (1.18–5.46)	1.62 (0.67–3.95)
Amount of phone use (operator recorded)[d]								
1st tertile	26	16	1.0	1.0	30	12	1.0	1.0
2nd tertile	15	30	0.31 (0.13–0.74)	0.32 (0.12–0.81)	25	20	0.50 (0.21–1.22)	0.55 (0.21–1.44)
3rd tertile	13	34	0.24 (0.10–0.57)	0.20 (0.07–0.54)	22	25	0.35 (0.15–0.85)	0.29 (0.10–0.83)

[a] Overestimation was defined as a ratio of self-reported to operator-recorded mobile phone use ≥ 1.5.
[b] Adjusted for all other variables included in the table.
[c] Low: elementary school not completed; intermediate: elementary school, high school or apprenticeship; high: university or technical college.
[d] 1st tertile: number of calls ≤ 173, duration of calls ≤ 327 minutes; 2nd tertile: number of calls 174–905, duration of calls 328–1228 min; 3rd tertile: number of calls >905, duration of calls >1228 min.

comparability with our study is limited because these study participants had a subscription that specified the maximum number of SMS allowed to be sent. Thus, awareness of use may be higher than for unrestricted subscriptions and there may also be a difference in remembering SMS in contrast to calls.

The pattern of overestimated low use and underestimated high use may be explained by the fact that there is an inherent difference in nature between the self-reported mobile phone use in CEFALO and the operator-recorded data. The participants in CEFALO were asked to estimate their mobile phone use in pre-defined categories while operators provided continuous traffic data. Because participants of CEFALO estimated their amount of mobile phone use on a categorical scale, extreme outliers could not occur. We believe that this design gives a more accurate estimation of past mobile phone use compared to estimation using open questions as it prevents the occurrence of extreme outliers as were discussed in the INTERPHONE study (INTERPHONE Study Group, 2010). Moreover, it is possible that participants may have had the tendency to avoid the most extreme response categories.

Virtually all of the studies that investigated mobile phone use and health outcomes among children and adolescents used self-reported amount of mobile phone use assessed by questionnaires or telephone surveys. The amount of mobile phone use is then often used to classify the participants into low- and heavy-users. This may be problematic and could have several important impacts on the results of these studies. Self-reported mobile phone use has been shown to be notoriously imprecise, even when it is short-term (Vrijheid et al., 2006a). Inaccurately reported mobile phone use could eventually lead to exposure misclassification and/or biased risk estimates (Armstrong, 1998; Aydin et al., 2011a; Vrijheid et al., 2006b). When exposure categories are used, random recall errors can lead to risk estimates biased towards and away from unity. It is noteworthy, however, that the proportion of non-regular mobile phone users in CEFALO was about 50% and thus considerable larger than in adult brain tumour studies (e.g. INTERPHONE, INTERPHONE Study Group, 2010). For non-regular users without a mobile phone subscription, operator recorded data could obviously not be retrieved. These non-regular users may indeed have barely used a mobile phone. If so, exposure misclassification is much lower in studies with children and adolescents compared to adult studies, as indicated by the high Spearman's rank correlation coefficients between self-reported and operator recorded mobile phone use when including non-users in the analysis.

Our study found little evidence that the likelihood of overestimating was higher among cases than controls. We found, however, evidence that other factors such as age and sex are associated with error in self-reporting of mobile phone use. Because such factors (as well as possibly others that we have not considered in our analysis) are also related to health, they may act as confounders in studies relying solely on self-reported mobile phone use.

4.2. Conclusions

Previous validation studies that assessed the accuracy of self-reported mobile phone use already provided evidence that studies based solely on self-reported amount of mobile phone use must be interpreted with caution, due to substantial reporting error. We emphasise the importance of including objective exposure data such as operator-recorded data or data from software modified phones (SMPs). Furthermore, we recommend the use of self-reported mobile phone use only in prospective studies. In this case, one should be aware that health-related factors are correlated with the amount of errors of reported use of mobile phones. Such factors would result in confounding and should be considered in the statistical analyses.

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3.3 Article 3: Persönliche Exposition durch hochfrequente elektromagnetische Felder in der Region Basel (Schweiz): Ein Überblick über die QUALIFEX-Studie

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Persönliche Exposition durch hochfrequente elektromagnetische Felder in der Region Basel (Schweiz): Ein Überblick über die QUALIFEX-Studie

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Zusammenfassung

Im Rahmen der QUALIFEX-Studie wurde bei Anwohnern der Region Basel die individuelle Exposition durch hochfrequente elektromagnetische Felder (HF-EMF) gemessen. Ein Ziel der Studie ist es, die Verteilung der HF-EMF-Exposition in der Bevölkerung zu erfassen und verschiedene Methoden der Expositionserhebung im Hinblick auf ihren Einsatz in epidemiologischen Studien zu evaluieren. Dazu wurden 166 Freiwillige mit tragbaren Exposimetern ausgestattet und ihre Exposition gegenüber HF-EMF während einer Woche gemessen. Zusätzlich wurde ein räumliches Ausbreitungsmodell entwickelt, um die durch ortsfeste Sendeanlagen verursachte Exposition in den Wohnungen der Studienteilnehmenden zu modellieren. In einer zufällig ausgewählten Bevölkerungsstichprobe (n = 1.375) wurden Daten zum Mobil- und Schnurlostelefongebrauch erhoben. Von einem Teil dieser Personen (n = 437) lagen die Mobilfunkverbindungsdaten der vorangehenden 4-6 Monate von den Mobilfunkanbietern vor. Die persönlichen Messungen der 166 Teilnehmenden ergaben eine mittlere HF-EMF Exposition von 0,22 V/m (Bereich: 0,07-0,58 V/m). Die Hauptbeiträge zur Gesamtbelastung stammten von Mobilfunkbasisstationen sowie Mobil- und Schnurlostelefonen. Die mit dem räumlichen Ausbreitungsmodell modellierte HF-EMF Exposition in den Wohnungen der Studienteilnehmenden korrelierte sowohl mit den entsprechenden Messwerten (Rangkorrelation: 0,72) als auch mit der gesamten wöchentlichen mittleren Exposition durch ortsfeste Sender an allen Aufenthaltsstandorten der Teilnehmenden (Rangkorrelation: 0,57). Der selbsteingeschätzte Gebrauch des Mobiltelefons korrelierte mit den Angaben der Netzbetreiber (Rangkorrelation: 0,78). Die QUALIFEX-Studie liefert wichtige Erkenntnisse über die Expositionsverteilung der Bevölkerung und für die Durchführung von epidemiologischen Studien. Um den zukünftigen technischen Entwicklungen Rechnung zu tragen, sollten solche Expositionsmessungen kontinuierlich weiter geführt und gegebenenfalls angepasst werden.

Schlagwörter: Epidemiologie, Expositionsabschätzung, hochfrequente elektromagnetische Felder (HF-EMF), Mobilfunk, Modellierung

Abstract

Personal radio frequency electromagnetic field exposure in Basel and area (Switzerland): An overview of the QUALIFEX project

Within the QUALIFEX project, personal radio frequency electromagnetic field (RF-EMF) exposure was measured. The aim of this publication is to give an overview of the RF-EMF exposure distribution in a Swiss population sample and to evaluate different exposure assessment methods regarding their application in epidemiological studies. Personal RF-EMF exposure of 166 volunteers from Basel, Switzerland, was measured during one week with portable exposure meters. In addition, a geospatial propagation model was developed to predict RF-EMF exposure from fixed site transmitters at study participants' residencies. Self-reported mobile and cordless phone use of a randomly selected population sample (n = 1.375) were collected and for a subsample (n = 437) objective operator data of network providers were available for the previous 4 to 6 months. Mean weekly exposure of all 166 volunteers was 0,22 V/m (range: 0,07-0,58 V/m). Total exposure was mainly due to mobile phone base stations, mobile phone handsets and cordless phones. Predicted exposure at home from the geospatial propagation model correlated with the corresponding measured mean exposure (rank correlation: 0,72) as well as with the measured mean exposure from fixed site transmitters at all places where study participants stayed during one week (rank correlation: 0,57). The rank correlation between self-reported mobile phone use and operator data was 0,78. The QUALIFEX study provides important information on the RF-EMF exposure distribution in the general population and for the conduct of epidemiological studies. With regard to future technical developments, it is important that exposure of the population is monitored continuously and that exposure assessment methods are adapted if necessary.

Keywords: epidemiology, exposure assessment, radio frequency electromagnetic field (RF-EMF), personal dosimeter, mobile phone

1 Hintergrund

Die zunehmende Nutzung von drahtlosen Kommunikationsmitteln wie Mobiltelefon, Schnurlostelefon oder Wireless LAN (kabelloses Internet) führt bei einem Teil der Bevölkerung zu Besorgnis. Dabei stehen negative Auswirkungen auf das subjektive Wohlbefinden wie Kopfschmerzen oder Schlafstörungen im Vordergrund (Schreier et al. 2006, Schröttner und Leitgeb 2008, Blettner et al. 2009). In zahlreichen wissenschaftlichen Publikationen konnten bisher keine eindeutigen Beweise gefunden werden (Hutter et al. 2006, Berg-Beckhoff et al. 2009), dass hochfrequen-

te elektromagnetische Felder (HF-EMF) die Gesundheit beeinträchtigen, wobei die Datenlage in Bezug auf langfristige alltägliche Expositionen immer noch sehr dürftig ist (Röösli 2008). Eine große Herausforderung bei der Erforschung von solchen langfristigen Auswirkungen ist die Abschätzung der Exposition.

Grundsätzlich können zwei Typen von HF-EMF Quellen unterschieden werden. Zum einen sind dies Quellen, die nahe am Körper (Nahfeld) zur Anwendung kommen und typischerweise vor allem am Kopf hohe, periodische und kurzzeitige Expositionen (z.B. Mobiltelefone) generieren. Zum anderen gibt es Fernfeldquellen, die tiefere, dafür kontinuierliche Ganzkörperexpositionen (z.B. Mobilfunkbasisstationen) verursachen. Neu entwickelte tragbare Dosimeter (Exposimeter) eignen sich für die Erfassung der Exposition im täglichen Leben unter Berücksichtigung, wo sich jemand aufhält. Exposimeter werden typischerweise in der Nähe einer Person deponiert oder unterwegs in einem Rucksack getragen. Sie liefern daher insbesondere aussagekräftige Resultate für quasi-homogene Felder von Fernfeldquellen.

In Bezug auf die Nahfeldquellen sind die Messwerte des Exposimeters jedoch wenig aussagekräftig, da die typische Nutzungsdistanz für diese Geräte viel kleiner ist als die Distanz zum Messgerät. Damit unterschätzen die Exposimetermessungen die Strahlenabsorption des Körpers. Die Exposition am Kopf wird auch bei nur sporadischer Nutzung von Schnurlos- und Mobiltelefonen von diesen Quellen dominiert (Neubauer et al. 2007, Frei et al. 2009, Viel et al. 2009). Entsprechend sind in epidemiologischen Studien Angaben über den Gebrauch von Schnurlos- und Mobiltelefonen für die Abschätzung von Nahfeldexposition nötig. Idealerweise handelt es sich dabei um objektive Daten von Telefongesellschaften. Diese sind aber nicht immer zugänglich, und in manchen Fällen lassen diese Daten nicht automatisch auf den Nutzer schließen (z.B. Geschäftstelefone, Familienanschlüsse), sodass der selbstberichtete Gebrauch auch eine wichtige Rolle bei epidemiologischen Studien spielt (Vrijheid et al. 2009).

Eine weitere Einschränkung des Exposimeters ist, dass bei einer großen Studienpopulation sowohl der zeitliche wie auch der finanzielle Aufwand sehr groß sind. Eine andere Möglichkeit, die Exposition durch Fernfelder abzuschätzen, sind daher räumliche Ausbreitungsmodelle. Bis jetzt gibt es aber erst wenige Ausbreitungsmodelle, die für den Einsatz in epidemiologischen Studien entwickelt wurden (Neitzke et al. 2007, Bürgi et al. 2008). Zudem ist unklar, ob und allenfalls wie stark die modellierte Exposition am Wohnort die Gesamtexposition einer Person im Alltag repräsentiert.

Im Rahmen der QUALIFEX-Studie (Gesundheitsbezogene Lebensqualität und Exposition gegenüber HF-EMF: eine prospektive Kohortenstudie) sammelten wir in einer Bevölkerungsstichprobe in der Region Basel (Schweiz) umfassende Daten zur Expositionssituation, sowohl von Fernfeldquellen wie auch von Nahfeldquellen. Dies beinhaltete persönliche Messungen während einer Woche bei 166 Freiwilligen (Exposimeterstudie), die Entwicklung eines räumlichen Ausbreitungsmodells für ortsfeste Sender (Modellierung) und den Vergleich von selbstberichteter Mobilfunknutzung mit Angaben der Netzbetreiber in einer Zufallsbevölkerungsstichprobe (Hauptstudie). Das Ziel dieser Publikation ist es, einen Überblick über die Expositionssituation einer schweizerischen Bevölkerungsstichprobe zu geben sowie verschiedene Expositionserhebungsmethoden im Hinblick auf den Einsatz in epidemiologischen Studien zu evaluieren.

2 Methodik

2.1 Persönliche Messungen in der Exposimeterstudie

166 Personen aus der Region Basel (Schweiz) haben für eine Woche ein Exposimeter mit sich herumgetragen und zusätzlich in einem Aktivitätstagebuch die entsprechenden Aufenthaltsorte eingetragen. Die Studienteilnehmenden waren mindestens 18 Jahre alt und wohnten in Basel und der Umgebung. Die Daten wurden zwischen April 2007 und Februar 2008 gesammelt. 131 Studienteilnehmende waren Freiwillige, die sich über unsere Homepage (*www.qualifex.ch*) oder per Telefon angemeldet haben. Die anderen 35 Teilnehmenden wurden aktiv rekrutiert, weil an ihrem Wohnort hohe Expositionen durch Mobilfunkbasisstationen oder durch Radio- und Fernsehstationen zu erwarten waren; entweder aufgrund unseres Ausbreitungsmodells (detaillierter Beschrieb siehe 2.2 "Räumliches Ausbreitungsmodell") oder aufgrund von Kontrollmessungen vom Lufthygieneamt beider Basel (LHA). Weil in einer randomisierten Bevölkerungsstichprobe hoch belastete Personen eher selten sind, haben wir diese hoch belasteten Personen speziell ausgesucht um, möglichst den ganzen Expositionsbereich in unserem Studiengebiet abdecken zu können. Das genaue Auswahlverfahren der Teilnehmenden der Exposimeterstudie ist in Frei et al. (2009) beschrieben. Für eine Validierungsstudie haben 31 Personen das Exposimeter drei bis 41 Wochen nach der Erstmessung während einer zweiten Woche nochmals mit sich herumgetragen.

Für die Messungen der individuellen HF-EMF Exposition wurden sieben Exposimeter EME Spy 120 (SATIMO, Courtaboeuf, France, *http://www.satimo.fr*) verwendet. Das Exposimeter kann in einem Messbereich von 0,05-5 V/m gleichzeitig zwölf verschiedene Frequenzbänder zwischen Radiostation (88–108 MHz) und W-LAN (2,4-2,5 GHz) messen (**Tab. 1**). Das Messintervall des Exposimeters be-

Tabelle 1: Verschiedene HF-EMF-Quellen mit deren Frequenzangaben, die mit dem Exposimeter EME Spy 120 gemessen werden können

Band	Abkürzung	Frequenz (MHz)	Beschreibung
FM	FM	88-108	FM Radiosender
TV3	TV	174-223	TV Fernsehsender
Tetrapol	Tetrapol	380-400	Mobiles Kommunikationssystem für Behörden
TV4/5	TV	470-830	TV Fernsehsender
GSM900 uplink	Mobiltelefon	880-915	Übertragung von Mobiltelefon zur Basisstation
GSM900 downlink	Mobilfunkbasisstation	925-960	Übertragung von Basisstation auf Mobiltelefon
GSM1800 uplink	Mobiltelefon	1710-1785	Übertragung von Mobiltelefon zur Basisstation
GSM1800 downlink	Mobilfunkbasisstation	1805-1880	Übertragung von Basisstation auf Mobiltelefon
DECT	DECT	1880-1900	Schnurlostelefon
UMTS uplink	Mobiltelefon	1920-1980	Übertragung von Mobiltelefon zur Basisstation
UMTS downlink	Mobilfunkbasisstation	2110-2170	Übertragung von Basisstation auf Mobiltelefon
W-LAN	W-LAN	2400-2500	Drahtlose Internetverbindung
Total			Summe aller Bänder

trug 90 Sekunden. Das Gerät wurde in einem Rucksack getragen oder für längere Aufenthalte in die Nähe der Person gestellt. Eine Studienassistentin instruierte die Studienteilnehmenden zu Hause und übergab ihnen ein Exposimeter, ein Aktivitätstagebuch und einen Fragebogen mit expositionsrelevanten Fragen. Im Aktivitätstagebuch wurden die Teilnehmenden aufgefordert, ihren Standort auf zehn Minuten genau zu dokumentieren und zusätzlich alle Telefonate mit dem Mobiltelefon und dem Schnurlostelefon ins Tagebuch einzutragen. Im Schlafzimmer jedes Teilnehmenden wurde zudem eine Messung (7-Punktemessung im Raum und 3-Punktmessung vor dem Schlafzimmerfenster) mit dem NARDA SRM-2000 Messgerät durchgeführt. Diese Messung wurde für die Validierung des Ausbreitungsmodells (siehe 2.2 "Räumliches Ausbreitungsmodell") verwendet.

Nach der Datenbereinigung (detailliert beschrieben in Frei et al. (2009)), wurde für jede Person ein wöchentlicher arithmetischer Mittelwert für jedes Frequenzband berechnet. Ein beträchtlicher Anteil der Messungen lag unterhalb der Nachweisgrenze des Gerätes (0,05 V/m). Deshalb erfolgten die Berechnungen der Mittelwerte mit der Methode der "robust regression on order statistics (ROS)" (Röösli et al. 2008). Eigene Telefonate mit dem Mobiltelefon oder dem Schnurlostelefon wurden für die Mittelwertberechnungen ausgeschlossen. Die berechneten Mittelwerte repräsentieren demzufolge primär die Exposition durch HF-EMF Fernfeldquellen.

Die statistischen Analysen wurden mit STATA Version 9.2 und 10.1 (StataCorp. College Station, TX, USA) und R Version 2.7.1 durchgeführt. Alle Berechnungen erfolgten in mW/m^2 (Leistungsflussdichte) und wurden danach in V/m umgerechnet.

2.2 Räumliches Ausbreitungsmodell

Um die Exposition durch ortsfeste Sender (Mobilfunkbasisstationen und Radio- und Fernsehstationen) am Wohnort der Studienteilnehmenden zu bestimmen, verwendeten wir ein numerisches Ausbreitungsmodell, das detailliert in Bürgi et al. (2008) und (2009) beschrieben ist.

Grundlage für die Modellierung ist eine Datenbank aller Sendeanlagen, welche vom LHA beider Basel erstellt wurde, und welche aus der Mobilfunk-Betriebsdatenbank des Bundesamts für Kommunikation mit den für ein bestimmtes Datum aktuellen Betriebsdaten ergänzt wurde. Ausgehend von diesen Daten (Position und Senderichtung der Antennen, Antennentypen und Abstrahlcharakteristik, mittlere Sendeleistung) berechnet das Ausbreitungsmodell die Stärke des HF-EMF für beliebige Punkte im Raum. Das Modell basiert auf semiempirischen Algorithmen, die ursprünglich für die Radioplanung der Netzbetreiber entwickelt wurden (durch COST und die International Telecommunications Union ITU) und berücksichtigt Schattenwurf und Beugung aufgrund der Topografie und der Bebauung in drei Dimensionen. Das Ausbreitungsmodell für QUALIFEX umfasst die Stadt Basel und den in der Schweiz liegenden Teil ihrer Umgebung (ca. 180 km^2 mit ca. 380.000 Einwohnern). Eingabedaten für das Modell sind außer der Antennendatenbank ein digitales Geländemodell und das dreidimensionale Gebäudemodell der Stadt Basel, ergänzt durch ein einfaches Blockmodell für die Gebäude außer-

halb der Stadt. Die Software für die Datenhaltung und Berechnung ist die erweiterte Version von NISMap (*www.arias.ch*). Für die Modellierung der HF-EMF im Innern von Gebäuden muss die Dämpfung und Reflexion an der Gebäudehülle und im Innern mitberücksichtigt werden. Da es in der Praxis aber unmöglich ist, die dafür nötigen Materialparameter für ein größeres Gebiet zu erfassen, verwendeten wir als einfachste Näherung einen konstanten mittleren Dämpfungsfaktor von 4,5 dB für alle Gebäude-Außenflächen (Wände, Fenster und Dächer) und einen konstanten Volumendämpfungsfaktor von 0,6 dB/m im Innern. Ausgabedaten des Ausbreitungsmodells sind einerseits farbkodierte Feldstärkekarten, andererseits wurden für die QUALIFEX-Studie gemittelte Feldstärken in der Wohnung der Studienteilnehmenden modelliert (als Mittelwert in einem Kreis von 5 m um ein gegebenes Zentrum, auf einer bestimmten Höhe innerhalb eines Gebäudes).

Das Ausbreitungsmodell wurde anhand der Punktmessungen mit dem NARDA SRM-3000 Messgerät im Schlafzimmer und vor dem Schlafzimmerfenster der Studienteilnehmenden der Exposimeterstudie validiert. Weitere Validierungsmessungen wurden in einer Messkampagne des LHA im Freien 1,5 m über Boden gemacht (Bürgi et al. 2009).

2.3 Mobil- und Schnurlostelefongebrauch in der Hauptstudie

Im Mai 2008 begann die Hauptstudie des QUALIFEX-Projekts. 4.000 Fragebögen wurden im Raum Basel (Schweiz) an zufällig ausgewählte Personen zwischen 30 und 60 Jahren verschickt. Der Fragebogen bestand aus verschiedenen Teilen. Es wurden Fragen über den Gesundheitszustand, über die Expositionssituation durch verschiedene Umweltfaktoren (z.B. Luftverschmutzung, Lärmbelästigung etc.) inklusive eigenem Mobiltelefon- und Schnurlostelefongebrauch, soziodemographische Faktoren (Alter, Ausbildung, Zivilstand) sowie Lifestylefaktoren (Rauchen, Größe, Gewicht, körperliche Aktivität) gestellt. Zusätzlich wurden die Teilnehmenden um das schriftliche Einverständnis gebeten, die Verbindungsdaten ihres Mobiltelefongebrauchs der letzten sechs Monate von den jeweiligen Netzbetreibern für statistische Auswertungen benützen zu dürfen. Bei Personen, die dieses Einverständnis gegeben haben, haben wir den selbstberichteten Gebrauch mit den objektiven Daten der Netzbetreiber verglichen.

Wir verglichen die Selbsteinschätzung der Teilnehmenden mit den Verbindungsdaten der Netzbetreiber bezüglich der Dauer des Mobiltelefongebrauchs in Minuten pro Woche. Das 50. und 90. Perzentil wurden benutzt, um die Daten in drei Expositionskategorien einzuteilen. Die Übereinstimmung zwischen den Kategorien wurde mit der linear gewichteten Kappa-Statistik von Cohen abgeschätzt, welche die Höhe der Übereinstimmung zwischen zwei Messgrößen jenseits des Zufalls auf einer Skala von -1 (perfekte Nichtübereinstimmung) und +1 (perfekte Übereinstimmung) misst. Das dazugehörige 95%-Vertrauensintervall (95%-VI) wurde durch Bootstrap mit 5.000 Replikationen berechnet. Die Übereinstimmung auf kontinuierlicher Skala wurde durch den Rangkorrelationskoeffizienten von Spearman quantifiziert.

Von einem der drei Netzbetreiber erhielten wir zusätzlich die Angaben, auf welchem Netz (GSM oder UMTS) die Telefonate durchgeführt wurden und ob es sich dabei um ein UMTS-fähiges Mobiltelefon handelt. Dies zu wissen ist aus der Sicht der Exposition entscheidend, da die mittleren Emissionen von UMTS-Telefonen etwa zwei Größenordnungen kleiner sind als bei GSM-Telefonen (Gati et al. 2009).

Ein Problem bei solchen Vergleichen ist, dass Personen, die angeben, kein Mobiltelefon zu besitzen, folglich keine Einverständniserklärung für einen Datentransfer von einem Mobilfunkbetreiber unterschreiben. Wenn man davon ausgeht, dass solche Personen tatsächlich kaum jemals ein Mobiltelefon benützen, führt der Ausschluss dieser Gruppe zu einer Unterschätzung der Übereinstimmung beim Vergleich der selbstberichteten Daten mit objektiven Daten, da man sich nur auf Mobiltelefonbenutzer konzentriert. Aus diesem Grund wurden alle Analysen zusätzlich unter der Annahme gemacht, dass Teilnehmende, die kein eigenes Mobiltelefon besitzen, eine objektive Mobiltelefongebrauchsdauer von 0 Minuten pro Woche bei den Netzbetreibern aufweisen würden.

3 Ergebnisse

3.1 Persönliche Messungen in der Exposimeterstudie

Das Durchschnittsalter der Studienteilnehmenden der Exposimeterstudie betrug 42,6 Jahre (**Tab. 2**). 55,4% der Personen waren Frauen.

Abbildung 1 zeigt die Verteilung der mittleren Exposition der 166 Studienteilnehmenden während einer Woche. Die mittlere Exposition durch HF-EMF ohne eigene Telefonate betrug 0,22 V/m. Die höchste gemessene wöchentliche mittlere Exposition durch HF-EMF eines Studienteilnehmenden war 0,58 V/m. Die kleinste mittlere Exposition lag bei 0,07 V/m.

Der größte Anteil aller Quellen an der Gesamtexposition (aller Studienteilnehmenden zusammen) waren Emissionen von Mobilfunkbasisstationen (32,0%). Das Mobiltelefon und das Schnurlostelefon (29,1% bzw. 22,7%) tru-

Tabelle 2: Charakterisierung der Studienpopulation der Exposimeterstudie und der Hauptstudie

	Exposimeterstudie		Hauptstudie	
	n	%	n	%
Geschlecht				
Männer	74	44,6	577	42,0
Frauen	92	55,4	798	58,0
Alter (Jahre)				
18–29	33	19,9	-	-
30–39	39	23,5	407	29,6
40–49	38	22,9	490	35,6
50–60	33	19,9	478	34,8
> 60	23	13,8	-	-
Ausbildung				
Keine Ausbildung/Obligatorische Schulzeit	2	1,2	89	6,5
Berufslehre	35	21,3	539	39,4
Maturitätsschule	18	11,0	124	9,1
Höhere Berufsbildung/Universität	109	66,5	615	45,0
Distanz Wohnort – nächste Mobilfunkantenne				
Distanz zur nächsten Mobilfunkantenne	227,5 m		278,5 m	
Wohnort				
Basel	89	53,6	539	39,2
Umgebung von Basel	77	46,4	836	60,8
Besitz von kabellosen Kommunikationsmitteln				
Personen mit einem Mobiltelefon	146	88,0	1283	93,7
Personen mit einem Schnurlostelefon	128	77,1	1132	82,3
Personen mit Wireless LAN	55	33,1	557	40,5

gen ebenfalls zu einem großen Teil zur Gesamtexposition bei. Die restliche HF-EMF wurde durch die Radio- und Fernsehstation (11,7%), durch Wireless LAN (4,1%) und durch TETRAPOL (0,3%) verursacht.

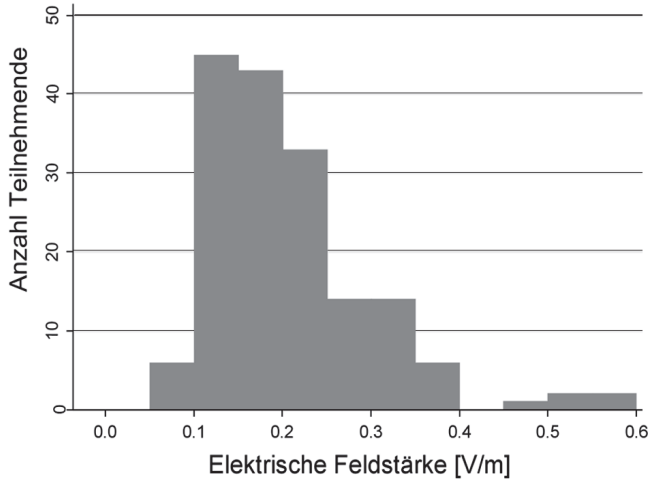

Abb. 1: Verteilung der mittleren Exposition (alle Quellen zusammen)

Wie in der Methodik erwähnt, haben wir für die Exposimeterstudie gewisse Personen speziell ausgewählt, weil sie aufgrund ihrer Wohnlage in der Nähe von Mobilfunkbasisstationen oder der Radio- und Fernsehstation speziell belastet sind (27 bzw. 8 Personen). Erwartungsgemäss dominierten bei diesen Personen die entsprechenden Quellen und sie zeigten eine höhere Gesamtexposition durch HF-EMF im Vergleich zu den nicht speziell ausgewählten Studienteilnehmenden (**Abb. 2**). Das nicht speziell ausgewählte Kollektiv (Freiwillige) verkörpert darum eher die durchschnittliche Expositionssituation im Studiengebiet. Bei diesen Personen stammte der Hauptanteil vom Mobiltelefon (39%), gefolgt vom Schnurlostelefon (24%) und von Mobilfunkbasisstationen (22%).

Besitzer eines Mobiltelefons hatten eine höhere Gesamtexposition (0,23 V/m) durch HF-EMF im Vergleich zu Personen, die kein eigenes Mobiltelefon besaßen (0,19 V/m), obwohl bei unseren Auswertungen die eigenen Telefonate nicht berücksichtig wurden. Dasselbe Bild ergab sich bei Personen, die ein Schnurlostelefon hatten (0,24 V/m vs. 0,20 V/m). Bei Personen, die zu Hause ein W-LAN besa-

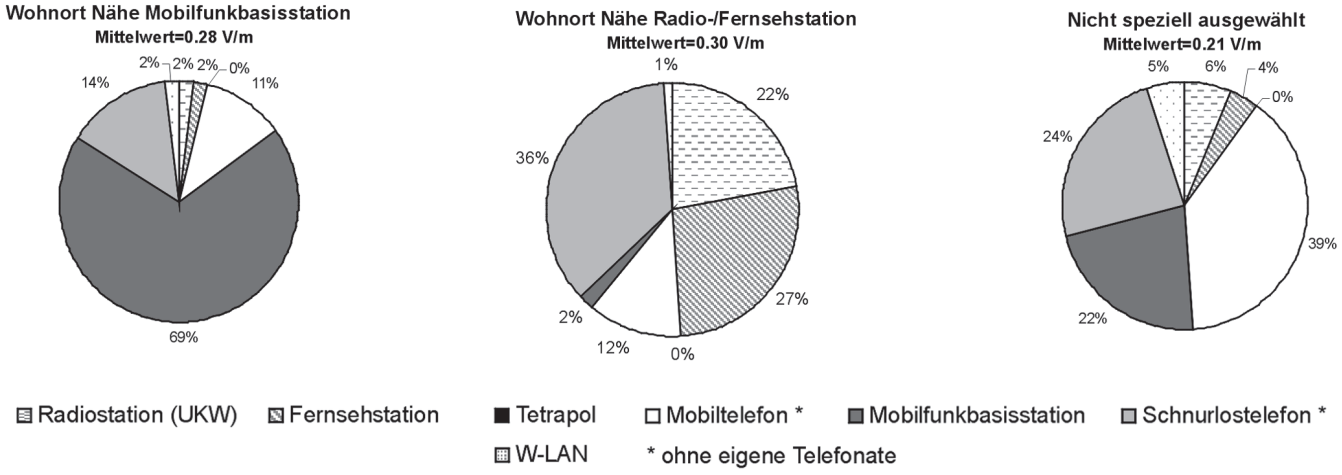

Abb. 2: Kuchendiagramme unterschieden nach Rekrutierungsstrategie; Beiträge der verschiedenen Strahlungsquellen in den spezifisch ausgewählten Gruppen (Wohnort Nähe Mobilfunkantenne, n = 27; Wohnort Nähe Radio-/Fernsehstationen, n = 8) und in der nicht speziell ausgewählten Gruppe (n = 131)

ßen, war entsprechend dieser Beitrag höher als für Personen ohne W-LAN (7,7% vs. 2,3%). Im Hinblick auf die Gesamtexposition spielte dieser Unterschied in der Strahlenexposition durch W-LAN aber keine große Rolle (mit W-LAN 0,23 V/m und ohne W-LAN 0,22 V/m) (Frei et al. 2009).

3.1.1 Räumliche Variabilität der Exposition

Die höchste mittlere HF-EMF Exposition wurde im Zug gemessen (0,66 V/m). Auch in Straßenbahnen und im Bus (0,37 V/m), während Autofahrten (0,29 V/m) und am Flughafen (0,53 V/m) wurden höhere Expositionen gemessen. Der größte Anteil an der Exposition hatte dabei das Mobiltelefon. Im Zug war 93,5% der Exposition auf das Mobiltelefon zurückzuführen. Relativ geringe mittlere Expositionen wurden in Schulgebäuden (0,09 V/m), in Kirchen (0,15 V/m), in Kinos, im Theater und während Konzerten (0,15 V/m) gemessen. Mobil- und Schnurlostelefone spielten in Schulgebäuden und Kirchen kaum eine Rolle und der Hauptbeitrag war durch Emissionen von Mobilfunkbasisstationen verursacht: 56,0% der Gesamtexposition in Schulhäusern und in Kindergärten und 70,2% in Kirchen.

3.1.2 Zeitliche Variabilität der Exposition

Die mittlere Exposition war am Tag (0,25 V/m) höher als in der Nacht (0,17 V/m) was hauptsächlich mit dem vermehrten Gebrauch von Mobiltelefonen anderer Personen zu erklären ist. Die Exposition während der Nacht wurde vor allem durch Mobilfunkbasisstationen (47,2%) verursacht. Es wurden hingegen keine Unterschiede in der mittleren Exposition zwischen den Wochentagen und dem Wochenende (beide 0,22 V/m) festgestellt.

3.1.3 Zweitmessungen

Bei 31 Personen wurde nach 3-41 Wochen eine Zweitmessung durchgeführt. Durchschnittlich lag in der zweiten Messwoche die mittlere Exposition tiefer als bei der Erstmessung (Median der Differenzen: -0,08 V/m). Für die Gesamtexposition war die Spearman'sche Rangkorrelation zwischen der ersten und zweiten Wochenmessung 0,61 (95%-KI: 0,32-0,79). Wurden nur die Erst- und Zweitmessungen zu Hause und im Schlafzimmer verglichen, betrug die Korrelation 0,74 (95%-VI: 0,52-0,87), respektive 0,81 (95%-VI: 0,63-0, 91) (Frei, et al. 2009). In **Abbildung 3** sind die Korrelationen der Erst- und Zweitmessungen an verschiedenen Orten dargestellt.

3.2 Räumliches Ausbreitungsmodell

Die modellierten Expositionen am Wohnort der Teilnehmenden der Exposimeterstudie variierten über zwei Größenordnungen (ca. 0,02-2 V/m). Die dominierenden Beiträge stammten dabei von GSM 1800 und GSM 900, kleinere Beiträge auch von UKW-Radio, UMTS und Fernsehstationen. Die Validierungsstudie mit den Messwerten des NARDA SRM-3000 Geräts fand für drei verschiedene Orte (Schlafzimmer, vor dem Schlafzimmerfenster, im Freien) Rangkorrelationskoeffizienten zwischen 0,64 und 0,67 (Bürgi et al. 2009).

Für eine Expositionsabschätzung basierend auf Terzilen ergaben sich Kappa-Werte zwischen 0,44 und 0,53. Interessanterweise waren die Resultate für das Modell im Gebäudeinnern (Schlafzimmer) fast gleich gut wie im Freien (Straße, Fenster). Diese Validierungsstudie wurde mit Kurzzeitmessungen unter standardisierten Bedingungen durchgeführt und zeigten, dass das Modell sowohl für Punkte im Freien

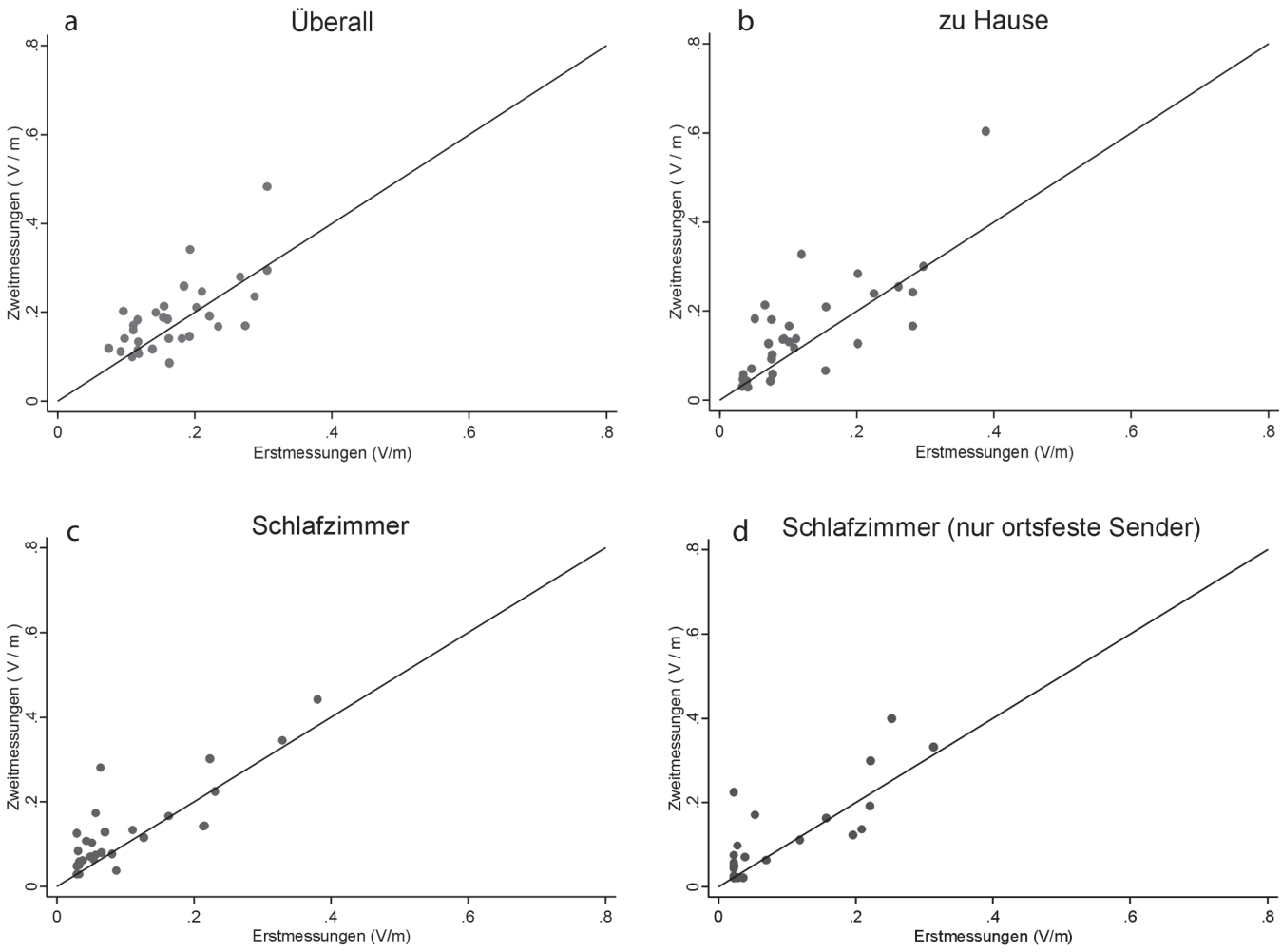

Abb. 3: Punktdiagramme der 1. und der 2. Messung in V/m mit der Exposition überall (a), der Exposition zu Hause (b), der Exposition im Schlafzimmer (c) und der Exposition im Schlafzimmer durch ortsfeste Sender (d). Die schwarze Linie markiert Werte der perfekten Übereinstimmung

wie auch für solche im Innern von Gebäuden gültige Resultate liefert. Aus epidemiologischer Sicht besonders interessant ist aber der Vergleich mit den über eine Woche gemittelten Resultaten der Exposimeterstudie. Das zeigt, wie gut die modellierte Exposition am Wohnort die Totalexposition repräsentiert. Dabei zeigt sich, dass die Rangkorrelation und das Kappa ungefähr gleich hoch wie bei der Validierungsstudie sind (**Tab. 3**). Interessanterweise war die Rangkorrelation höher als bei der Validierungsstudie, wenn nur die Exposition durch ortsfeste Anlagen am Wohnort der

Tabelle 3: Vergleich zwischen dem modellierten HF-EMF durch ortsfeste Sendeanlagen in der Wohnung der Studienteilnehmenden und verschiedenen Exposimetermessungen (Mittelwerte). ρ_s ist der Spearman-Korrelationskoeffizient, κ_3 der Kappa-Koeffiziernt für eine Klassifikation in drei Terzile. Der Koeffizient κ_{90} sowie die Sensitivität und Spezifität wurden für Trennpunkte beim 90. Perzentil berechnet

	Exposimeter: nur Bänder für ortsfeste Sender			Exposimeter: alle Messbänder		
	Überall	**Zu Hause***	**Schlafzimmer**	**Überall**	**Zu Hause**	**Schlafzimmer**
ρ_s	0,57	0,72	0,65	0,28	0,46	0,51
κ_3	0,42	0,52	0,48	0,15	0,30	0,32
κ_{90}	0,52	0,65	0,38	0,45	0,45	0,38
Sensitivität	0,56	0,69	0,44	0,50	0,50	0,44
Spezifität	0,95	0,97	0,94	0,95	0,95	0,94

* Man beachte, dass sich nur in dieser Kolonne Messung und Modellierung auf das Gleiche beziehen (Exposition zu Hause durch ortsfeste Sender)

Tabelle 4: Vergleich der selbstberichteten durchschnittlichen Dauer des Mobiltelefongebrauchs in Minuten pro Woche mit den Angaben der Netzbetreiber. Zusätzlich sind noch die selbstberichteten Angaben des Gesamtkollektivs bezüglich des Mobiltelefongebrauchs (n = 1.327) und des Gebrauchs von Schnurlostelefonen (n = 1.367) aufgelistet

	N	Mittelwert (Min./Woche)	Median (Min./Woche)	IQR (Min./Woche)	Maximum (Min./Woche)
Gesamtkollektiv					
Selbstberichtet Mobiltelefongebrauch	1327	67,9	13,5	55,0	1785,0
Selbstberichtet Schnurlostelefongebrauch	1367	75,7	21,0	105,0	560,0
Mobiltelefongebrauch: Personen mit objektiven Angaben					
Selbstberichtet	437	61,9	13,5	35,0	1785,0
Netzbetreiber	437	34,0	13,4	31,7	516,3
Mobiltelefongebrauch: Personen mit objektiven Angaben inkl. Personen die angaben kein Mobiltelefon zu besitzen					
Selbstberichtet	524	51,6	9,0	26,0	1785,0
Netzbetreiber	524	28,4	9,1	27,4	516,3

Studienteilnehmenden (r_s=0,72) berücksichtigt wurden. Diese höhere Übereinstimmung im Vergleich mit der Validierungsstudie ist wohl darauf zurückzuführen, dass die Modellierung einen zeitlichen Mittelwert abbildet. Die Kurzzeitmessungen der Validierungsstudie unterliegen aber einer zeitlichen Variabilität, die eine zusätzliche Streuung in den Daten verursacht, die bei den wöchentlichen Exposimetermessungen nicht auftritt.

Selbst bei Berücksichtigung aller Frequenzbänder war die Modellierung mit der persönlichen HF-EMF Exposition korreliert (**Tab. 3**). Die Korrelation zwischen der modellierten Exposition durch ortsfeste Sendeanlagen in der Wohnung im Vergleich zum gemessenen Wochenmittelwert (alle Quellen) betrug 0,28. Entsprechend zeigte die modellierte Exposition eine Sensitivität von 0,5 und eine Spezifität von 0,95 bei einem Trennpunkt beim 90. Perzentil.

3.3 Mobil- und Schnurlostelefongebrauch in der Hauptstudie

Von den 1.375 retournierten Fragebögen der Hauptstudie haben 1.327 Personen Angaben über ihren Mobiltelefongebrauch und 1.367 Personen Angaben über ihren Schnurlostelefongebrauch gemacht. Für 437 Teilnehmende waren sowohl die Selbsteinschätzung des Mobil- und Schnurlostelefongebrauchs vom Fragebogen als auch die Mobilfunkverbindungsdaten von den Netzbetreibern vorhanden.

Die Teilnehmenden der Hauptstudie gaben im Durchschnitt an 67,9 Minuten pro Woche mit einem Mobiltelefon zu telefonieren und 7,5 Minuten länger mit einem Schnurlostelefon (**Tab. 4**). Der durchschnittliche selbstberichtete Mobiltelefongebrauch von den 437 Personen mit Netzbetreiberdaten war 61,9 Minuten verglichen mit 34,0 Minuten gemäß Netzbetreiber. Hingegen unterschied sich die mediane Anzahl Minuten Mobiltelefongebrauch pro Woche kaum zwischen Selbsteinschätzung und den Angaben der Netzbetreiber. Dieses Resultat ändert sich nicht, wenn man Personen mit einschließt, die angaben, kein Mobiltelefon zu besitzen. Der Kappa-Koeffizient zwischen selbsteingeschätztem wöchentlichen Mobiltelefongebrauch und Netzbetreiberangaben war 0,41 (95%-VI: 0,33-0,49, n = 437). Der entsprechende Rangkorrelationskoeffizient betrug 0,63 (95%-VI: 0,57-0,68, n = 437) (**Abb. 4**). Schließt

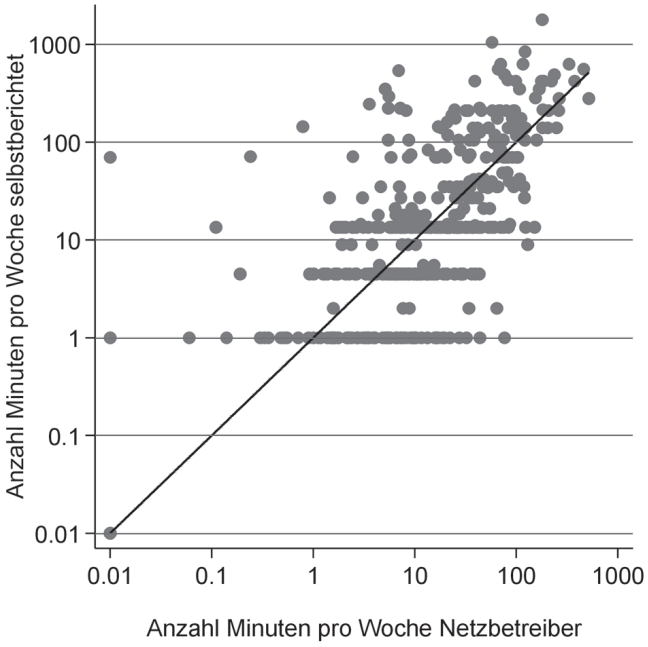

Abb. 4: Streudiagramm der logarithmierten wöchentlichen Dauer des Mobiltelefongebrauchs in Minuten pro Woche selbsteingeschätzt und Angaben der Netzbetreiber. Die schwarze Linie markiert Werte der perfekten Übereinstimmung (n = 524). (Werte von 0 wurden mit 0,01 ersetzt, um den Logarithmus berechnen zu können)

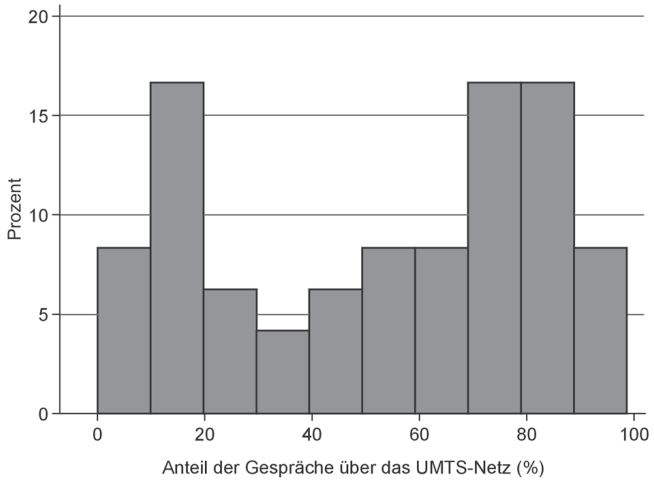

Abb. 5: Prozentsatz der privaten Gespräche, die bei einem bestimmten Anteil über das UMTS-Netz geführt wurden (n = 47)

man diejenigen Personen ein, die angaben, kein Mobiltelefon zu benutzen, erhöhte sich die Übereinstimmung (Kappa = 0,51, 95 %-VI: 0,45-0,58, n = 524) und der Rangkorrelationskoeffizient von 0,78 (95 %-VI: 0,75-0,81, n = 524).

Insgesamt gaben 179 (13,0%) Teilnehmende der Hauptstudie an, ein UMTS-Telefon zu besitzen. 928 (67,5%) Teilnehmende gaben an, kein UMTS-Telefon zu besitzen und 268 (19,5%) gaben an, es nicht zu wissen. Die Übereinstimmung zwischen der Selbsteinschätzung, ob man ein UMTS-fähiges Mobiltelefon besitzt und den entsprechenden Angaben der Mobilfunkbetreiber, war in einer Untergruppe, wo wir die entsprechenden objektiven Angaben hatten, moderat (Kappa = 0,44, 95 %-VI: 0,27-0,61, n = 207). So hatten nur 17 von 31 Personen, die angaben ein UMTS-Telefon zu besitzen, tatsächlich ein solches Telefon benutzt. Interessanterweise erfolgten auch bei einem UMTS-fähigen Mobiltelefon längst nicht alle Gespräche über das UMTS-Netz, obwohl die Benutzung von UMTS beim entsprechenden Netzbetreiber zum Studienzeitpunkt priorisiert wurde (**Abb. 5**).

4 Diskussion

Ziel dieser Publikation war es, die Exposition durch HF-EMF bei einer Bevölkerungsstichprobe in der Region Basel zu charakterisieren sowie verschiedene Expositionserfassungsmethoden zu evaluieren. Die totale gemessene mittlere Exposition durch alle HF-EMF Quellen lag in unserer Stichprobe bei 0,22 V/m. Am meisten trugen Emissionen von Mobilfunkbasisstationen, von Mobiltelefonen und von Schnurlostelefonen zur Gesamtexposition bei. Das räumliche HF-EMF-Ausbreitungsmodell zeigte eine gute Übereinstimmung mit den Punktmessungen des NARDA SMR-3000 und den Exposimetermessungen und korrelierte sogar mit der gesamten wöchentlichen Exposition der Studienteilnehmenden.

Unsere Messkampagne hat gezeigt, dass die mittlere totale Exposition deutlich geringer ist als die von der ICNIRP empfohlenen Grenzwerte (ICNIRP 1998). Beim Vergleich mit den Grenzwerten ist aber zu beachten, dass sich die Grenzwerte auf zeitliche und örtliche Maxima beziehen, während wir mit dem Exposimeter Durchschnittswerte erhoben haben. Dies gilt auch für die speziell ausgewählten Personen, die in der Nähe von Mobilfunkbasisstationen oder Radio-/Fernsehstationen wohnen. Unsere Resultate sind im Allgemeinen vergleichbar mit anderen Studien. So haben Viel et al. (2009) eine ähnliche mittlere Exposition mit demselben Gerätetyp und einer ähnlichen statistischen Methode (robust regression on order statistics) in einem Studienkollektiv von 377 zufällig ausgewählten Personen in Frankreich gemessen. Dort betrug die mittlere Exposition 0,201 V/m. Berechnen wir die mittlere Exposition von denjenigen Personen in der Exposimeterstudie, die wir nicht speziell ausgewählt haben (n = 131), so ergibt sich eine praktisch identische mittlere Exposition (0,204 V/m). Die höchsten Expositionen wurden in der französischen Studie durch das Schnurlostelefon, das W-LAN und die Radiosender gemessen. In unserer Studie war die Exposition vor allem durch Schnurlostelefone, Mobilfunkbasisstationen und Mobiltelefone dominiert. Dies ist insofern interessant, als dass die Schweizer Anlagegrenzwerte für Emissionen von Mobilfunkbasisstationen tiefer sind als die ICNIRP-Referenzgrenzwerte, die in Frankreich gelten. Von daher hätte man eher erwartet, dass der Anteil von Mobilfunkbasisstationsstrahlung in Frankreich größer ist als in der Schweiz. Dies war aber nicht der Fall. Bei uns war die mittlere Exposition durch Basisstationen beim unselektierten Kollektiv 0,096 V/m, in der französischen Zufallsstichprobe 0,044 V/m. Es stellt sich also die Frage, ob ein dichteres Mobilfunkbasisstationsnetz zu höheren mittleren Expositionen führt, oder ob diese Unterschiede auf andere Gründe zurückzuführen sind. Auch bei Thomas et al. (2008) lag die mittlere Exposition weit unter den ICNRIP-Grenzwerten. Die mittlere Exposition lag dabei zwischen 0,13% und 0,58% der ICNIRP-Grenzwerte. Allerdings mussten die Nachtmessungen aus den Analysen ausgeschlossen werden und es wurden nur drei Frequenzbereiche gemessen: GSM900, GSM1800 (inkl. UMTS und DECT) und W-LAN.

Auffällig bei unseren Resultaten ist der hohe Expositionsbeitrag durch Mobiltelefone (39% bei den nicht-selektierten Probanden), obwohl wir Messungen von der Analyse ausgeschlossen haben, wenn im Tagebuch vermerkt war, dass selber telefoniert wurde. Somit repräsentieren diese Messungen entweder Telefonate benachbarter Personen, organisatorische Kommunikation des eigenen Mobiltele-

fons (z.B. Übergabe der Kommunikation zwischen zwei Basisstationen bei Zellenwechsel) oder es handelt sich um eigene Telefonate, die nicht im Tagebuch notiert wurden. Aufgrund unserer Daten lässt sich nicht bestimmen, wie groß die jeweiligen Anteile sind. Sollte sich jedoch bestätigen, dass ein substanzieller Beitrag der persönlichen HF-EMF-Exposition von Mobiltelefonen benachbarter Personen stammt, wäre dies vergleichbar mit der Situation beim Rauchen bzw. Passivrauchen. Natürlich sind die Gesundheitsimplikationen beim heutigen Kenntnisstand für Rauchen und HF-EMF-Strahlung deutlich unterschiedlich.

Im Hinblick auf zukünftige epidemiologische Forschung konnten durch diese verschiedenen Expositionsabschätzungsmethoden wichtige Erkenntnisse gewonnen werden:

Erstens zeigte sich, dass es möglich ist, mithilfe von Exposimeter und Aktivitätstagebuch wertvolle Daten über die Expositionssituation der Bevölkerung zu sammeln. Es zeigte sich aber auch, dass solche Messungen hohe Ansprüche an die Studienteilnehmenden stellen und eine hohe Motivation voraussetzen. Das bedeutet, dass die direkte Anwendung zur Expositionsabschätzung in epidemiologischen Studien limitiert ist, da bei einer Zufallsbevölkerungsstichprobe wohl ein erheblicher Teil der Personen die Teilnahme verweigern würde. Das hätte einen Selektionsbias zur Folge, wenn die Verweigerung abhängig vom Gesundheitszustand und der Exposition ist. Zudem ist zu beachten, dass bei der direkten Expositionsabschätzung mit dem Exposimeter, die Messungen einfach manipuliert werden können, indem man das Messgerät absichtlich in die Nähe von HF-EMF-Quellen stellt. Aus diesem Grund wurden in der QUALIFEX-Studie die Expositionserhebungen in einem separaten Kollektiv durchgeführt. Die Teilnehmenden der Exposimeterstudie hatten also keine Motivation die Messergebnisse zu beeinflussen.

Eine zweite wichtige Erkenntnis der Studie war, dass sich die mittlere persönliche HF-EMF-Exposition während einer Woche auch Monate später mit einer Zweitmessung noch reproduzieren lässt. Das war nicht a priori zu erwarten, da HF-EMF in der Umwelt eine große zeitliche und räumliche Heterogenität aufweisen. Der Grund für die Reproduzierbarkeit liegt in erster Linie darin, dass die Expositionssituation am Wohnort entscheidend zur durchschnittlichen Exposition beiträgt. Es scheint, dass im Alltag alle Personen ähnlich exponiert sind, aber die Exposition am Wohnort entscheidend zwischen hoch und tief Exponierten diskriminiert. Zu Hause verbringt man einen großen Teil seiner Zeit und die Expositionssituation bleibt relativ konstant. Da diese erheblich von den Emissionen von ortsfesten Sendeanlagen beeinflusst ist, erklärt sich auch, warum die Sensitivität und Spezifität der Expositionsmodellierung von ortsfesten Sendeanlagen mit dem Ausbreitungsmodell sich praktisch nicht verändern, wenn man es mit der gemessenen Totalexposition von allen Quellen vergleicht (**Tab. 3**).

Drittens konnte die Studie damit zeigen, dass sich die Exposition durch ortsfeste Sender am Wohnort modellieren lässt und sogar mit der mittleren gemessenen HF-EMF-Exposition während einer Woche über alle Frequenzen korreliert. Das bedeutet, dass im Prinzip alleine mit einem solchen Modell gewisse Expositionsdiskriminierungen möglich sind. Natürlich ist der Fehler in der Expositionsabschätzung größer als bei einer Expositionsabschätzung, die zusätzliche individuelle expositionsrelevante Aspekte mitberücksichtigt, wie beispielsweise den Besitz eines Schnurlostelefons (Frei et al. 2009). Dafür erfordert eine Modellierung keine Teilnahmebereitschaft von Studienteilnehmenden, sodass von dieser Seite bei einer epidemiologischen Studie kein Selektionsbias zu erwarten ist. Zusätzlich kann mit einem Modell mit wenig Zusatzaufwand die Exposition für ein deutlich größeres Studienkollektiv modelliert werden und es ist auch möglich historische Exposition oder Langzeitexpositionen abzuschätzen, wenn die entsprechenden Inputdaten vorliegen. In einer bereits publizierten Studie von Neitzke et al. (2007) wurde auch ein Ausbreitungsmodell für eine epidemiologische Studie entwickelt. In dieser Studie konnten nur Daten von Mobilfunkbasisstationen (keine Daten von Radio- und Fernsehstationen) als Inputdaten verwendet werden. Dieses Modell wurde danach in einer epidemiologischen Studie angewendet (Breckenkamp et al. 2008). Dabei hat sich gezeigt, dass die Qualität und Präzision der Inputdaten sehr wichtig ist. Diese Erkenntnis bestätigen auch unsere Ergebnisse (Bürgi et al. 2009).

Viertens zeigte sich, dass die Übereinstimmung von selbstberichteter Mobilfunknutzung und objektiven Netzbetreiberangaben relativ gut war. Dennoch stellt sich die Frage, ob bei epidemiologischen Studien der Fehler zufällig verteilt ist oder abhängig vom Gesundheitsstatus ist. Im Rahmen dieser Studie lässt sich das nicht bestimmen. Falls Letzteres zutrifft, ist ein Bias bei der Analyse der Expositions-Wirkungsbeziehung zu erwarten. Falls Kranke ihren Gebrauch überschätzen, würde ein falsch-positives Resultat resultieren; bei Unterschätzung ein falsch-protektiver Effekt. Im Hinblick auf zukünftige Studien kommt erschwerend dazu, dass viele Leute nicht wissen, ob sie ein UMTS-Telefon besitzen. Und sogar falls bekannt, ist unklar, wie häufig tatsächlich auf dem UMTS-Netz telefoniert wird.

Mit den Expositionsmessungen im Rahmen der QUALIFEX-Studie konnten wichtige Erkenntnisse über die Expositionssituation der Bevölkerung gewonnen werden. Insgesamt lässt sich feststellen, dass immer noch sehr wenig über die typische Exposition der Allgemeinbevölkerung im Alltag

bekannt ist. Bisherige Messkampagnen fokussierten häufig auf Orte, wo hohe Messwerte zu erwarten sind und haben nicht berücksichtigt, wo und wie lange sich Personen typischerweise aufhalten. Ein besseres Verständnis der Exposition der Allgemeinbevölkerung erlaubt eine effizientere Planung zukünftiger epidemiologischer Studien, eine bessere Interpretation der Ergebnisse der bisherigen Studien und bildet die Grundlage für Risikoabschätzung auf Populationsebene. Es ist aber auch zu berücksichtigen, dass alle diese Erkenntnisse vorübergehender Natur sind. Die technische Entwicklung ist rasch und dies wird die Expositionssituation der Bevölkerung verändern. Aus diesem Grund ist es wichtig, dass Expositionsmessungen und Modellierungen kontinuierlich weiter geführt und gegebenenfalls den neuen Umständen angepasst werden.

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4 Mobile phone use and risk of brain tumors among children and adolescents

4.1 Article 4: Mobile phone use and brain tumors in children and adolescents

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ARTICLE

Mobile Phone Use and Brain Tumors in Children and Adolescents: A Multicenter Case–Control Study

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Background It has been hypothesized that children and adolescents might be more vulnerable to possible health effects from mobile phone exposure than adults. We investigated whether mobile phone use is associated with brain tumor risk among children and adolescents.

Methods CEFALO is a multicenter case–control study conducted in Denmark, Sweden, Norway, and Switzerland that includes all children and adolescents aged 7–19 years who were diagnosed with a brain tumor between 2004 and 2008. We conducted interviews, in person, with 352 case patients (participation rate: 83%) and 646 control subjects (participation rate: 71%) and their parents. Control subjects were randomly selected from population registries and matched by age, sex, and geographical region. We asked about mobile phone use and included mobile phone operator records when available. Odds ratios (ORs) for brain tumor risk and 95% confidence intervals (CIs) were calculated using conditional logistic regression models.

Results Regular users of mobile phones were not statistically significantly more likely to have been diagnosed with brain tumors compared with nonusers (OR = 1.36; 95% CI = 0.92 to 2.02). Children who started to use mobile phones at least 5 years ago were not at increased risk compared with those who had never regularly used mobile phones (OR = 1.26, 95% CI = 0.70 to 2.28). In a subset of study participants for whom operator recorded data were available, brain tumor risk was related to the time elapsed since the mobile phone subscription was started but not to amount of use. No increased risk of brain tumors was observed for brain areas receiving the highest amount of exposure.

Conclusion The absence of an exposure–response relationship either in terms of the amount of mobile phone use or by localization of the brain tumor argues against a causal association.

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A steep rise in the popularity of mobile phones among children and adolescents in recent years has been reflected in both increased ownership and increased usage (1–3). One study (4) has indicated that most children start to use mobile phones when they are around 9–10 years old, but usage before school age is not uncommon. The increase in mobile phone use has raised concerns about possible adverse health effects. Brain tumors have been a main concern because when the handset is held to the head, the brain absorbs most of the radio frequency energy emitted by mobile phones. Moreover, it has been hypothesized (5) that children may be more vulnerable to radio frequency electromagnetic fields (RF EMFs) because they have a developing nervous system, their brain tissue is more conductive than that of adults (because of its higher water content and ion concentration), and RF EMFs penetrate into regions that are deeper in their brains [because the head circumference is smaller in children compared with adults (5)]. Recent modeling studies (6,7) have indicated that about twice as much mobile phone energy is absorbed in the peripheral brain tissues of children aged 5–8 years as in adults.

The radio frequency radiation emitted by mobile phone handsets has insufficient energy to directly damage DNA: It is nonionizing and its only known effect is heating. Hence, genotoxic effects such as DNA mutations or strand breaks cannot be directly linked to exposure to mobile phone radiation (8). The lack of genotoxicity of mobile phone radiation has been confirmed by experimental animal and laboratory studies (9,10). Overall, in vitro studies and experiments in mice [reviewed in (11)] have provided little evidence that mobile phone radiation is carcinogenic.

To date, no study has addressed the association between mobile phone use and the risk of brain tumors among children and adolescents. Studies in adults have shown no increase in risk among regular users but have been inconclusive regarding longer-term

heavy use of mobile phones (12). The recently published INTERPHONE study (13) found an increased risk for glioma among heavy users (cumulative call duration ≥ 1640 hours), but it is uncertain whether this reflects a true risk associated with the use of mobile phones or a spurious relationship due to recall bias or other methodological limitations (13,14). A study by Hardell et al. (15) reported that astrocytoma was much more common among adults who first used mobile phones before age 20 (odds ratio [OR] = 5.2) or who first used cordless phones before age 20 (OR = 4.4).

In 2006, we set up CEFALO, an international case–control study of the relationship between mobile phone use and risk of developing brain tumors in children and adolescents. Participants were children aged 7–19 years in Denmark, Sweden, Norway, and Switzerland. We collected data by means of face-to-face interviews with the subjects and their parents.

Subjects and Methods

Study Population

CEFALO is an international case–control study performed in Denmark, Sweden, Norway, and Switzerland. The study period was approximately from January 1, 2004, through August 31, 2008, but varied slightly between study centers.

Case Eligibility and Ascertainment

All children and adolescents who were diagnosed during the study period with intracranial central nervous system tumors and who were aged 7–19 years at the time of diagnosis were eligible to become case patients. The brain tumors had to be coded as C71, D33.0–33.2, D33.9, D43.0–43.2, D43.9, or C72.9 according to the *International Classification of Diseases, tenth revision* (*ICD-10*) to be included. In addition, they had to fulfill the diagnostic criteria according to following morphology codes from the *International Classification of Diseases for Oncology, third edition* (*ICD-O-3*): ependymoma (9383, 9391–9393), astrocytoma (9384, 9400–9401, 9410–9411, 9420–9424, 9440–9442), primitive neuroectodermal tumor (PNET; 9470–9474, 9480, 9502–9504, 9508), other glioma (9380–9382, 9430, 9444, 9450–9451, 9460), other specified intracranial neoplasms (8743, 9064, 9071, 9080, 9161, 9390, 9412–9413, 9492–9493, 9505–9507, 9560), or unspecified intracranial neoplasms (8000–8005, 9990, 9999).

All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. We examined medical records for case patients to confirm the diagnosis and to establish the date of diagnosis, which was used as reference date in the exposure assessment. Date of diagnosis was defined as the date when the first diagnostic imaging was performed. Case patients were excluded if they were diagnosed with neurofibromatosis (Mb Recklinghausen; 12 patients) or tuberous sclerosis (one patient). Study participants who were completely deaf before the reference date and children with severe mental retardation were excluded (two patients and two control subjects). In addition, families with insufficient language skills to complete an interview, as judged by a nurse, treating physician, or project administrator, were excluded (15 patients and 36 control subjects).

Each country established procedures for identification of the case patients. In Denmark and Sweden, case identification was performed by a combination of reports from pediatric, oncology, and neurosurgery departments and from the population-based registries (the Danish National Cancer Registry, Childhood Cancer Registry, Pathology Registry, and National Patient Registry, and the Swedish Regional Cancer Registries, which also provide the data for the Swedish National Cancer Registry). In Norway, all case patients were identified from the population-based Norwegian National Cancer Registry and verified by the responsible physician. In Switzerland, case patients aged younger than 16 years at diagnosis were identified through the Swiss Childhood Cancer Registry, and case patients aged 16–19 years at diagnosis were identified through neurosurgery clinics, pathology departments, and cantonal general cancer registries.

Control Eligibility and Selection

We randomly selected two control subjects per case patient using population registries in the participating countries, matched by age (in Denmark, Sweden, and Switzerland, by year and month of birth; in Norway, by year of birth), sex, and geographical region. In Switzerland, a two-stage random sampling procedure was applied for the selection of control subjects in the absence of a national population registry. First, a community was randomly determined within the same language region as each patient, and second, the control subject was randomly selected from the

CONTEXT AND CAVEATS

Prior knowledge

No previous studies have examined whether mobile phone use among children and adolescents is associated with a difference in brain tumor risk.

Study design

The study included all 352 patients aged 7–19 who were diagnosed with brain tumors in 2004–2008 in Denmark, Sweden, Norway, or Switzerland and 646 age-, sex-, and region-matched controls. Mobile phone use was determined from interviews and, when available, from operator records. Odds ratios were determined for brain tumor incidence.

Contribution

Mobile phone users had no statistically significant difference in brain tumor risk compared with nonusers. Risk did not increase with the duration of mobile phone use. Nor was risk higher in the areas of the brain that came into closest proximity to a hand-held mobile phone.

Implications

The authors found little or no evidence that mobile phones increase brain tumor risk, and the single positive association could be explained by bias or chance.

Limitations

Most mobile phone usage data were based on the recall of children or adolescents and their parents. Brain tumors are rare, and the study was not statistically powered to detect small risk increases. Amount and duration of mobile phone use was relatively small and may have increased in this age-group since the time of this study.

From the Editors

corresponding communal population registry. The reference date for control subjects was same as the date of diagnosis of the matched case patient.

Data Collection

Data collection started in June 2006 in all countries except Norway, where data collection started in December 2007. All case patients for whom physicians authorized contact and all control subjects were informed about the study and asked to participate (we did not receive authorization from the physicians of 19 case patients). The information letter explained the study focus on risk factors for brain tumors and did not mention mobile phones to minimize differential participation bias. The procedures varied between countries, depending on the requirements of local ethics review boards. If the case patient was deceased (36 cases), the parents were contacted at least 6 months after the death of the child, as requested by the treating physicians. The case patients and control subjects provided signed informed consent in all countries.

Whenever possible, the children were accompanied by at least one parent (preferably the mother) and were interviewed face to face by trained interviewers using a computer-assisted personal interview (CAPI) questionnaire (Denmark and Norway) or a paper version of the questionnaire (Switzerland and Sweden). In exceptional circumstances, telephone interviews were conducted with difficult-to-reach subjects (four control subjects) or an adapted paper version of the questionnaire was sent to the study participants (19 control subjects). Interviews with case patients and matched control subjects were mainly performed by the same interviewer. Interviewers from all centers received training at a joint workshop to ensure uniform data collection. The translations of the questionnaires were checked through back-translation to the master version (English), and the questionnaires were pilot tested in all participating countries. At all centers, control subjects who refused to participate in the study (n = 172) were asked to complete a short nonresponder questionnaire (85 were completed). A small number of nonparticipating case patients (n = 8) also completed the nonresponder questionnaire. Due to local ethical guidelines, it was not possible to send nonresponder questionnaires to case patients in Denmark when written refusals were received from case families. All case patients were interviewed within 5 years of diagnosis, and 63% were interviewed within 2 years of diagnosis.

Mobile Phone Exposure Assessment

All study participants were asked if they had ever spoken on a mobile phone more than 20 times during their lives and if the child ever owned a mobile phone before the reference date. Owners of a mobile phone were asked how many subscriptions they have had. For each subscription, the following information was asked: network operator, when the subscription was started and stopped, use of hands-free devices, preferred side of head during use, number of calls per day, and duration of calls (both in predefined categories of use). Major changes in usage within a subscription were also recorded.

For calculating exposure surrogates, we did not consider mobile phone use that occurred within 6 months before the reference date. All subjects who had an average of at least one call per week for at least 6 months based on their self-reported amount of phone use were classified as regular users of mobile phones (16). Additional calculated exposure variables for regular users were time since first use of mobile phones (years), cumulative duration of subscriptions (years), cumulative duration of use (hours), and cumulative number of calls. All cumulative exposure surrogates were corrected for the use of hands-free devices. For all time periods for which the subject reported the use of hands-free devices, the amount of phone use was reduced by 80%, 50%, or 20% depending on whether hands-free devices were used almost always, half of the time, or sometimes, respectively.

Study participants were asked to give consent to allow the researchers access to traffic data from mobile phone network operators. Data was provided by two network operators in Sweden, three in Denmark, and three in Switzerland. Operators were asked for data linked to a specific personal identification number, phone number or name, or a combination of any of the data given by the study participants. From the network operators, we received information about number of calls, duration of calls, as well as subscription start and end dates. In Switzerland, traffic data is deleted after 6 months. Thus, only data covering the period after the reference date were available in Switzerland. Only time since first subscription of phones could be used from the operator recorded data from Switzerland because this date is not routinely deleted.

Statistical Analysis

Odds ratios and 95% confidence intervals (CIs) were based on conditional logistic regression models for matched case–control studies (17). All statistical tests were two-sided. In the main analyses, the reference category for odds ratios consisted of subjects who were nonregular users or nonusers of mobile phones. Time since first use of mobile phones, cumulative duration of subscriptions, cumulative duration, and number of calls were categorized based on the distribution of these variables in control subjects who were regular users; the 50th and 75th percentiles were chosen as cutoffs to allow for the skewed data distribution. *P* values for tests of linear trend (in risk for brain tumors in relation to exposure) were calculated by means of a two-sided Wald test for regression models in which exposure was included as a continuous variable, and all subjects in a category were assigned the median value of their corresponding category (18).

We checked the impact of the following potential confounders on our analyses: highest attained educational level of either mother or father as a measure of socioeconomic status (SES; low: elementary school not completed; intermediate: elementary school, diploma school, or apprenticeship; high: university or technical college), family history of cancer (yes, no), past medical radiation exposure to the head (yes, no), maternal smoking during pregnancy (yes, no), past head injuries (yes, no), use of baby monitors (ie, wireless baby monitor or alarm used to remotely listen to sounds made by an infant) near the head (yes, no), use of cordless phones (cumulative duration and number of calls), contact with animals (yes, no), location where the child lived before age 6 (town or village with ≥200 inhabitants, farm, countryside), having siblings (yes, no), birth weight (continuous), born premature (yes, no), ever doctor-diagnosed asthma (yes, no), ever doctor-diagnosed atopic eczema (yes, no), and ever doctor-diagnosed hay fever (yes, no). We decided a priori to include confounders in our model if the odds ratio for the regular use of mobile

phones changed by 10% or more compared with the unadjusted model (19,20). Because none of the confounders that we considered changed the risk estimate for regular use of mobile phones by 10% or more, none of these confounders were included in the conditional logistic regression models presented.

To evaluate consistency of the results, we conducted analyses that were stratified by country, age-group (<15and ≥15 years), sex, tumor morphology (astrocytoma and other glioma compared with all other tumors), tumor location (highly exposed temporal, frontal lobes, and cerebellum compared with other parts of the brain), time between diagnosis and interview (≥1.5 and <1.5 years), time lag between interview of case patients and matched control subjects (>50 and ≤50 days), and latency periods of 2 and 5 years. Heterogeneity of the odds ratios between the strata was assessed with a likelihood ratio test that compared models that included only the main effects with those that included the interaction terms for the stratum-specific associations (21).

For the subset of subjects for whom operator data were available, analyses were made using the network operator recorded data to assess exposure. We used unconditional logistic regression models adjusted for geographical region, age and sex with operator recorded time since first subscription, cumulative duration of subscription, and, cumulative duration and number of calls as exposure variables. For the same subset of subjects, and for subjects for whom no operator recorded data were available, we also calculated unconditional logistic regression models using self-reported mobile phone use as exposure estimates, to compare the results for these two subsets of participants, and to allow an assessment of potential recall bias in self-reported mobile phone use.

In additional analyses, we compared the side of the head where users preferred to hold their mobile with the side of the head in which the tumor occurred by applying the method used in the INTERPHONE study (13). Each control subject was assigned the location of the tumor of the corresponding matched case patient. We considered the exposure to be ipsilateral if the phone was used predominantly on the same side as the tumor or on both sides of the head. We considered the exposure to be contralateral if the phone was used mostly on the side of the head opposite to the tumor. No laterality was assigned if the tumor was centrally located, and separate analyses were made with these subjects.

We also analyzed the potential relationship between other sources of radio frequency exposure and the risk for brain tumors. Specifically, we analyzed whether subjects ever used baby monitors near the head, ever used cordless phones, and the cumulative duration and number of calls with cordless phones in the first 3 years of use.

The software Stata/SE, version 10.1 (StataCorp, College Station, TX), was used for all analyses (22).

Time Trend Analysis

Because usage of mobile phones among children and adolescents has been a relatively recent and rapidly increasing phenomenon, we compared our study results with the observed time trends of brain tumor incidence. Most recent incidence data from among the four participating countries were available from Sweden (http://www.socialstyrelsen.se/statistik/statistikdatabas; accessed May 27, 2011). We used the observed brain tumor incidence data of Swedish children and adolescents aged 5–19 years from 1990 to 2008 and added hypothetical incidence rate trends derived from our risk estimates for regular mobile phone use based on self-reported and operator recorded data and estimated exposure prevalence (23). The proportion of regular mobile phone users was estimated by combining data from the control subjects in CEFALO with subscriber data in Sweden (http://www.itu.int/ITU-D/ict/; accessed May 27, 2011).

Results

In total, 423 case patients and 909 potential control subjects were identified during the study period. Interviews were completed with 352 (83.2%) eligible case patients and 646 (71.1%) eligible control subjects. The participation rates among case patients ranged from 65.7% in Norway to 97.7% in Denmark and among control subjects from 58.2% in Norway to 76.3% in Sweden. The main reasons for nonparticipation were refusal to participate (18 case patients and 172 control subjects), inability to contact the subject (five case patients and 70 control subjects), and physicians' denial of permission to contact some patients due to the severity of their disease (19 case patients). The median age of the study participants overall was 13 years and 46% were female (Table 1).

Among the 352 case patients, 162 (46.0%) were diagnosed with an astrocytoma, 21 (6.0%) with ependymoma, 30 (8.5%) with another glioma, 62 (17.6%) with primitive neuroectodermal tumors, 53 (15.1%) with other specified intracranial neoplasms, and 24 (6.8%) with unspecified intracranial neoplasms.

Use of Mobile Phones

There were 265 (75.3%) case patients and 466 control subjects (72.1%) who reported having spoken on a mobile phone more than 20 times before the time when the case patient was diagnosed. Regular mobile phone use was reported by 194 (55%) case patients

Table 1. Characteristics of case patients and control subjects

Characteristic	Case patients (n = 352) No. (%)	Control subjects (n = 646) No. (%)
Country		
Denmark	85 (24.1)	170 (26.3)
Sweden	138 (39.2)	228 (35.3)
Norway	44 (12.5)	78 (12.1)
Switzerland	85 (24.1)	170 (26.3)
Age at reference date, y*		
7–9	88 (25.0)	167 (25.9)
10–14	144 (40.9)	265 (41.0)
15–19	120 (34.1)	214 (33.1)
Sex		
Female	162 (46.0)	293 (45.4)
Male	190 (54.0)	353 (54.6)
Highest educational level of parents†		
Low	20 (5.7)	26 (4.0)
Intermediate	188 (53.4)	336 (52.0)
High	144 (40.9)	279 (43.2)
Unknown	0 (0)	5 (0.8)

* Age at diagnosis for case patients and matched control subjects.

† Low: elementary school not completed; intermediate: elementary school, high school, or apprenticeship; high: university or technical college.

and 329 (51%) control subjects. Brain tumor patients were not statistically significantly more often regular mobile phone users compared with control subjects (OR = 1.36; 95% CI = 0.92 to 2.02; Table 2). We also looked at various other exposure surrogates and observed somewhat elevated odds ratios without a clear exposure–response relationship for the following exposure variables: time since first use (P_{trend} = .37), cumulative duration of subscriptions (P_{trend} = .14), cumulative duration of calls (P_{trend} = .42), and cumulative number of calls (P_{trend} = .58). Children who started to use mobile phones at least 5 years ago were not at increased risk compared with those who had never regularly used mobile phones (OR = 1.26, 95% CI = 0.70 to 2.28; Table 2).

For regular use of mobile phones, a stratified analysis by country yielded odds ratios greater than 1 for all countries except Norway (Table 3), although the observed pattern was in line with random variability (*P* for heterogeneity = .20). In stratified analyses according to age at diagnosis (<15 and ≥15 years), sex, tumor location, tumor morphology, and time difference between case and control interviews, the odds ratios of regular use of mobile phones were not statistically significantly different between the strata.

We found no elevated risk among regular users of mobile phones when we looked at the parts of the brain with the highest radio frequency exposure, that is, the temporal and frontal lobes and the cerebellum (Table 3). On the other hand, we did find a statistically significant odds ratio for tumors in the parts of the brain with the lowest exposure to radiation among regular users of mobile phones (OR = 1.92; 95% CI = 1.07 to 3.44).

Operator Recorded Data

To confirm the results that we obtained from questionnaires, we also analyzed data on phone use, when available, from the mobile phone companies. Operator recorded data regarding the amount of time that had elapsed since the phone users' first subscriptions were activated were available for 35% of case patients and 34% of control subjects who reported to have a mobile phone subscription. For this subset of subjects, we found a statistically significantly increased risk among users with the longest period since first subscription (OR = 2.15 [95% CI = 1.07 to 4.29] among 24 case patients and 25 control subjects who had subscriptions for more than 2.8 years, P_{trend} < .001; Table 4). We also tabulated records for cumulative duration of subscription, cumulative hours of use, and cumulative number of calls. For each of these categories, exposure–response trends were not statistically significant. Risk estimates based on self-reported data were similar for the subset of subjects for whom operator data were available compared with the corresponding risk estimates in the subset with no operator data.

Laterality of Mobile Phone Use

Because the absorbance of radiation from a mobile phone is highly localized to the side of the head where the phone is held, we also examined laterality of mobile phone use and occurrence of brain tumors. The odds ratio for brain tumor risk among ipsilateral regular users of mobile phones was not higher than the odds ratio of contralateral regular users (OR = 1.74, 95% CI = 0.91 to 3.33 and

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) of brain tumors associated with mobile phone use*

Variable	Case patients, No.	Control subjects, No.	OR (95% CI)	P_{trend}†
Regular use‡				
No§	158	317	1.0 (referent)	
Yes	194	329	1.36 (0.92 to 2.02)	
Time since first use, y				.37
Never regular user	158	317	1.0 (referent)	
≤3.3	95	165	1.35 (0.89 to 2.04)	
3.3–5.0	53	83	1.47 (0.87 to 2.49)	
>5.0	46	81	1.26 (0.70 to 2.28)	
Cumulative duration of subscriptions, y§				.14
Never regular user	158	317	1.0 (referent)	
≤2.7	94	163	1.34 (0.89 to 2.01)	
2.8–4.0	45	78	1.45 (0.83 to 2.54)	
>4.0	52	81	1.58 (0.86 to 2.91)	
Cumulative duration of calls, h§				.42
Never regular user	158	317	1.0 (referent)	
≤35	94	162	1.33 (0.89 to 2.01)	
36–144	48	81	1.44 (0.85 to 2.44)	
>144	49	81	1.55 (0.86 to 2.82)	
Cumulative number of calls§				.58
Never regular user	158	317	1.0 (referent)	
≤936	94	163	1.34 (0.89 to 2.02)	
937–2638	50	80	1.47 (0.86 to 2.51)	
>2638	47	79	1.42 (0.79 to 2.53)	

* Mobile phone use was defined as regular use, time since first use, cumulative duration of subscriptions, cumulative duration of calls, and cumulative number of calls.

† *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

‡ "Regular use" was defined as use of a mobile phone at least once per week for a period of 6 months or more.

§ Six observations were dropped from the analysis because four participants had missing exposure data.

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for stratified analyses

	Regular use*					
	No†			Yes		
Stratum	Case patients n	Control subjects n	OR (95% CI)	Case patients n	Control subjects n	OR (95% CI)
Main analysis (for comparison)	158	317	1.0 (referent)	194	329	1.36 (0.92 to 2.02)
By country						
Denmark	36	78	1.0 (referent)	49	92	1.49 (0.61 to 3.61)
Sweden	57	109	1.0 (referent)	81	119	1.73 (0.87 to 3.41)
Norway	21	31	1.0 (referent)	23	47	0.51 (0.18 to 1.41)
Switzerland	44	99	1.0 (referent)	41	71	1.69 (0.79 to 3.61)
By age-group, y‡						
<15	146	292	1.0 (referent)	86	140	1.42 (0.89 to 2.26)
≥15	12	25	1.0 (referent)	108	189	1.23 (0.59 to 2.58)
By sex						
Female	61	123	1.0 (referent)	101	170	1.52 (0.81 to 2.84)
Male	97	194	1.0 (referent)	93	158	1.27 (0.76 to 2.11)
By time between diagnosis and interview, y§						
≥1.5	122	257	1.0 (referent)	133	244	1.10 (0.75 to 1.61)
<1.5	35	60	1.0 (referent)	61	85	1.53 (0.68 to 3.43)
By time between cases' and controls' interviews						
Both controls within 50 d	69	151	1.0 (referent)	89	165	1.46 (0.81 to 2.62)
One or more controls >50 d	89	166	1.0 (referent)	105	164	1.29 (0.75 to 2.20)
By tumor location						
Temporal, frontal lobes, and cerebellum	83	155	1.0 (referent)	98	178	1.00 (0.58 to 1.72)
Other than temporal, frontal lobes, and cerebellum	75	162	1.0 (referent)	96	151	1.92 (1.07 to 3.44)
By tumor morphology						
Astrocytoma and other glioma	84	160	1.0 (referent)	108	189	1.14 (0.66 to 1.97)
All except astrocytomas and other glioma	74	157	1.0 (referent)	86	140	1.65 (0.93 to 2.93)
By latency time, y						
2	222	436	1.0 (referent)	130	210	1.34 (0.90 to 1.99)
5	319	601	1.0 (referent)	33	45	1.36 (0.77 to 2.40)

* "Regular use" was defined as use of a mobile phone at least once per week for a period of 6 months or more.

† Reference category.

‡ Age of patients at diagnosis and comparable age for matched control subjects.

§ Based on unconditional logistic regression adjusted for geographical region, sex, and age.

OR = 2.07, 95% CI = 0.95 to 4.52, respectively; Table 5). For all exposure surrogates except time since first use of mobile phones, odds ratios of contralateral use in the highest exposure category were larger than the odds ratios for ipsilateral use. For those excluded from the laterality inverse exposure–response associations were observed.

Other Radio Frequency Electromagnetic Field Exposure Sources

We also evaluated other potentially relevant sources of radio frequency electromagnetic fields in early life. We found no evidence for a relationship between ever use of baby monitors near the head and brain tumor risk (OR = 0.96, 95% CI = 0.50 to 1.86; Table 6). In addition, children's use of cordless phones was not related to brain tumor risk (for the group with the highest amount of cordless phone use [>70 hours], OR = 1.18, 95% CI = 0.65 to 2.14; Table 6).

Evaluation of Time Trends

We also examined the age-adjusted brain tumor incidence rates among Swedish children and adolescents aged 5–19 years from 1990 to 2008 including hypothetical incidence rate trends (Figure 1). In these estimates, we made the assumption that regular use of mobile phones increases the risk of brain tumors by 36% (based on self-reported exposure; Table 2) or 115% after 3 years of regular mobile phone use (based on operator recorded exposure; Table 4). A risk estimate of 2.15 after 3 years of regular mobile phone use is expected to increase the incidence rate by about 50% in the last 10 years based on the proportion of regular users in our study collective. No such trend was observed in the incidence rates; in fact, rather the opposite trend was observed. This indicates that short-term use of mobile phone does not cause brain tumors in children and adolescents.

Discussion

The CEFALO study is the first case–control study of use of mobile phones and brain tumor risk in children and adolescents to our knowledge. Our primary analysis does not point to a statistically significantly increased risk for brain tumors in children that is associated with the use of mobile phones. There was no consistent exposure–response relationship either in terms of the amount of mobile phone use or by the location of the tumor. In a small subset of study participants with operator recorded data (n = 163),

Table 4. Comparison of analyses with operator-recorded and self-reported mobile phone use

	Operator recorded use				Self-reported use in collective with available operator data				Self-reported use in collective without available operator data			
	Case patients	Control subjects			Case patients	Control subjects			Case patients	Control subjects		
Variable	n	n	OR (95% CI)	P_{trend}*	n	n	OR (95% CI)	P_{trend}*	n	n	OR (95% CI)	P_{trend}*
Time since first subscription, y				.001				.25				.22
Never regular user†	134	259	1.0 (referent)		127	245	1.0 (referent)		154	305	1.0 (referent)	
≤1.8	19	51	0.78 (0.43 to 1.40)		33	62	1.09 (0.65 to 1.84)		59	103	1.17 (0.79 to 1.74)	
1.8–2.8	19	25	1.71 (0.85 to 3.44)		17	25	1.47 (0.69 to 3.14)		30	57	1.15 (0.67 to 1.97)	
>2.8	24	25	2.15 (1.07 to 4.29)		19	28	1.51 (0.68 to 3.35)		36	54	1.47 (0.81 to 2.67)	
Cumulative duration of subscriptions, y				.15				.62				.18
Never regular user†	133	259	1.0 (referent)		125	239	1.0 (referent)		155	311	1.0 (referent)	
≤1.8	13	26	1.14 (0.55 to 2.37)		21	36	1.24 (0.66 to 2.33)		73	128	1.19 (0.82 to 1.72)	
1.9–3.3	10	13	1.73 (0.71 to 4.20)		8	15	1.17 (0.44 to 3.13)		37	67	1.23 (0.74 to 2.05)	
>3.3	11	13	1.84 (0.74 to 4.58)		12	21	1.19 (0.47 to 3.03)		40	61	1.46 (0.83 to 2.55)	
Cumulative duration of calls, h				.36				.85				.47
Never regular user†	133	259	1.0 (referent)		125	239	1.0 (referent)		155	311	1.0 (referent)	
≤11	14	26	1.24 (0.61 to 2.55)		23	34	1.50 (0.79 to 2.83)		71	130	1.14 (0.79 to 1.65)	
12–27	11	13	1.95 (0.81 to 4.73)		7	21	0.70 (0.27 to 1.81)		41	61	1.48 (0.89 to 2.47)	
>27	9	13	1.38 (0.53 to 3.61)		11	17	1.27 (0.46 to 3.49)		38	65	1.36 (0.77 to 2.40)	
Cumulative number of calls				.60				.74				.57
Never regular user†	133	259	1.0 (referent)		125	239	1.0 (referent)		155	311	1.0 (referent)	
≤573	16	26	1.43 (0.71 to 2.88)		21	32	1.51 (0.78 to 2.92)		73	132	1.15 (0.79 to 1.66)	
574–1292	11	13	1.79 (0.74 to 4.29)		8	21	0.71 (0.28 to 1.79)		42	61	1.51 (0.91 to 2.51)	
>1292	7	13	1.08 (0.38 to 3.06)		12	19	1.34 (0.53 to 3.35)		35	63	1.24 (0.71 to 2.16)	

* *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

† Reference category (among never regular users, 123 cases and 233 control subjects reported to have no subscription and were included as references in all analyses).

Table 5. Association between brain tumors and mobile phone use by side of phone use*

Variable	Ipsilateral use				Contralateral use				Central or unknown location			
	Case patients n	Control subjects n	OR (95% CI)	P_{trend}†	Case patients n	Control subjects n	OR (95% CI)	P_{trend}†	Case patients n	Control subjects n	OR (95% CI)	P_{trend}†
Regular use‡												
No	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
Yes	62	83	1.74 (0.91 to 3.33)		49	63	2.07 (0.95 to 4.52)		68	135	0.74 (0.40 to 1.39)	
Time since first use, y				.08				.08				.08
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤3.3	29	40	1.73 (0.87 to 3.44)		24	36	1.86 (0.82 to 4.21)		36	68	0.81 (0.41 to 1.57)	
3.3–5.0	15	25	1.53 (0.62 to 3.76)		16	16	3.27 (1.10 to 9.68)		19	31	0.82 (0.34 to 1.94)	
>5.0	18	18	2.75 (0.93 to 8.06)		9	11	2.39 (0.67 to 8.57)		13	36	0.36 (0.13 to 1.02)	
Cumulative duration of subscriptions, y				.02				.03				.01
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤2.7	28	44	1.54 (0.78 to 3.05)		23	35	1.83 (0.81 to 4.15)		37	60	0.90 (0.48 to 1.69)	
2.8–4.0	14	19	2.38 (0.84 to 6.80)		13	17	2.67 (0.88 to 8.11)		15	32	0.44 (0.17 to 1.15)	
>4.0	20	20	3.74 (1.19 to 11.77)		12	9	4.00 (1.11 to 14.41)		15	40	0.23 (0.07 to 0.74)	
Cumulative duration of calls, h				.14				.03				.02
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤35	28	48	1.46 (0.74 to 2.91)		19	35	1.65 (0.73 to 3.74)		40	59	0.97 (0.50 to 1.85)	
36–144	17	17	2.66 (1.05 to 6.71)		13	17	4.14 (1.25 to 13.66)		15	37	0.43 (0.18 to 1.03)	
>144	17	18	2.64 (0.92 to 7.59)		16	9	6.19 (1.57 to 24.35)		12	36	0.24 (0.08 to 0.73)	
Cumulative number of calls				.08				.06				.02
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤936	30	46	1.59 (0.81 to 3.12)		22	38	1.74 (0.78 to 3.90)		37	57	0.98 (0.51 to 1.92)	
937–2638	13	19	2.06 (0.72 to 5.93)		14	12	5.37 (1.54 to 18.72)		17	38	0.54 (0.24 to 1.23)	
>2638	19	18	2.91 (1.09 to 7.76)		12	11	4.82 (1.21 to 19.24)		13	37	0.31 (0.11 to 0.87)	

* All matched sets in which the case patient and/or the control subject was a regular contralateral user were excluded from the ipsilateral analyses; similarly, sets in which the case patient and/or the control subject was a regular ipsilateral user were excluded from the contralateral analyses. CI = confidence intervals; OR, odds ratio.

† *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

‡ "Regular use" was defined as use of a mobile phone at least once per week for a period of 6 months or more.

Table 6. Odds ratios (ORs) and 95% confidence intervals (CIs) of brain tumors associated with other radio frequency electromagnetic field exposure sources*

Variable	Case patients No.	Control subjects No.	OR (95% CI)	P_{trend}*
Ever use of baby monitors† near the head				
No	335	611	1.0 (referent)	
Yes	17	35	0.96 (0.50 to 1.86)	
Ever use of cordless phones				
No	110	216	1.0 (referent)	
Yes	242	430	1.09 (0.81 to 1.45)	
Cumulative duration of calls with cordless phones, h‡				.20
Never user of cordless phones	102	189	1.0 (referent	
≤23	70	135	0.98 (0.65 to 1.46)	
24–70	39	60	1.15 (0.71 to 1.87)	
>70	25	38	1.18 (0.65 to 2.14)	
Missing	116	224	0.94 (0.67 to 1.32)	
Cumulative number of calls with cordless phones‡,§				.20
Never user of cordless phones	102	189	1.0 (referent)	
≤235	61	116	1.01 (0.66 to 1.53)	
236–704	48	79	1.07 (0.68 to 1.69)	
>704	27	39	1.21 (0.68 to 2.15)	
Missing	114	223	0.94 (0.67 to 1.31)	

* *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

† Wireless baby monitor or alarm to remotely listen to sounds made by an infant.

‡ In the first 3 years of use.

§ The 75th and 90th percentiles served as cutoffs because of broad categories.

however, time since the start of a mobile phone subscription was statistically significantly related to brain tumor risk.

Because of the methodological limitations of retrospective case–control studies and the absence of a known biological mechanism for carcinogenicity by low-dose microwave radiation, we considered several measures of exposure and conducted various stratified and sensitivity analyses to evaluate the consistency of our findings. Most results of these analyses were in line with the primary analysis and did not indicate an increased risk. However, we did observe a statistically significant trend of increasing risk with increasing time since first subscription when we used the data recorded by the network operators (Table 4). There was no

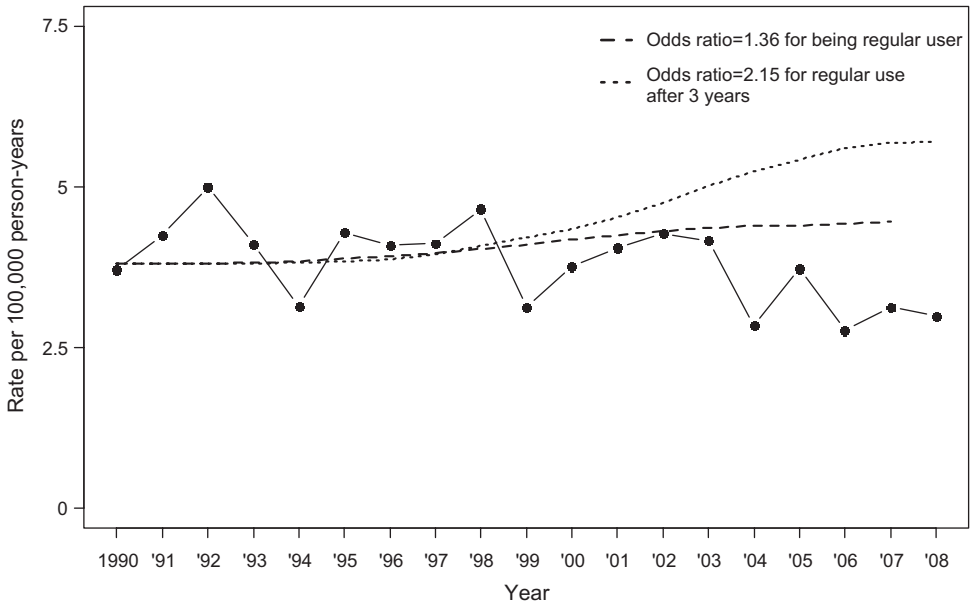

Figure 1. Gender and age-standardized incidence rates among Swedish children and adolescents aged 5–19 years between 1990 and 2008 (solid line). **Dotted lines** denote hypothetical incidence rate trends under the assumption that regular use of mobile phones increases the risk for brain tumors by 36% (odds ratio [OR] = 1.36) (without considering a latency period) and by 115% (OR = 2.15) after 3 years of regular mobile phone use (based on risk estimates in Tables 2 and 4), respectively.

consistent trend with cumulative duration or number of calls. Operator recorded data are considered more reliable and less prone to recall bias than self-reported exposure data. However, our data were limited because we obtained operator recorded time since first subscription from only 35% of case patients and 34% of control subjects who reported to own a subscription. These proportions were even smaller for the other operator recorded exposure surrogates. In addition, operator data themselves have limitations. For example, the children had to remember their phone number(s) for us to be able to link to the operator data, and we still had to rely on interviews to account for whether recorded calls were made or taken with the use of hands-free devices. Also, we could obviously not verify from operator data whether the children themselves or others were using the mobile phone for any given recorded call. It is quite likely that the child occasionally lent out his or her phone to a peer or, in contrast, borrowed a phone from someone else. For underage study participants, subscriptions were sometimes held in the name of the parents and disentangling of the actual user(s) of each subscription may sometimes have been erroneous.

Reverse causality is another aspect to consider when interpreting the observed increased risk for time since first subscription. Reverse causality exists if the condition of having a brain tumor itself prompted the use of mobile phones and thus the exposure of interest. For example, because of prodromal symptoms before diagnosis, some case patients may have appeared frailer than healthy children (24,25). To provide frail children better protection, parents may have given them a mobile phone to use in case of emergency or to keep in contact with friends in a situation with reduced mobility.

To estimate recall bias, we compared self-reported and objective mobile phone use data (26). We found that the duration and number of calls were overestimated by case patients (median ratio = 1.09, interquartile range [IQR] = 0.47–2.27 for number of calls and median ratio = 1.52, IQR = 0.63–4.28 for duration of calls) and control subjects (median ratio = 1.34, IQR = 0.63–5.36 for number of calls and median ratio = 2.63, IQR = 0.89–10.06 for duration of calls). The average extent of overestimation was not statistically significantly different between case patients and control subjects, suggesting that there was no substantial recall bias; however, the confidence limits were wide.

Because we did not find a clear exposure–response relationship in most of these analyses, the available evidence does not support a causal association between the use of mobile phone and brain tumors. Furthermore, some results of our sensitivity analyses make a causal relationship appear to be unlikely. For instance, odds ratios for brain tumors in analyses restricted to case patients with tumors in the temporal and frontal lobes and the cerebellum were not increased compared with odds ratios from the corresponding main analyses. If there was a causal relationship, we would expect an increased risk specifically in these regions because the absorption of radio frequency energy from mobile phones is highly localized and has been shown to be considerably higher in the temporal and frontal lobes and the cerebellum compared with other parts of the brain (27). In fact, in laterality analyses, we found a higher risk for contralateral tumors than for ipsilateral tumors relative to where mobile phones were held and even found fewer tumors with a central or an unknown location, whereas if a causal relationship existed, highest risk for ipsilateral tumors would be expected (28). However, the number of participants in this analysis was small and confidence intervals were large. In addition, subjects' statements about which side of the head they preferred to hold the mobile phone near during its use are often considered unreliable as was discussed in the INTERPHONE study (13).

Hardell and colleagues [eg, (15)] consistently found estimates of brain tumor risk to be of the same order of magnitude for both uses of mobile and cordless phones. In this study, however, we found no statistically significantly increased risk for brain tumors in relation to cordless phone use.

Our study has several strengths. Participation rates were high for case patients (83.2%) and for control subjects (71.1%) compared with other case–control studies on mobile phone use and brain tumors in adults (13). Most importantly, when we used a logistic regression model to analyze the nonresponder interviews of control subjects by assessing the participation probabilities of users and nonusers of mobile phones, we did not find that the probability of participation was different between mobile phone users and nonusers according to case or control status [data not shown, see (26) for details]. Thus, the occurrence of relevant selection bias is unlikely in the CEFALO study.

To assess the possibility of confounding, we collected information on the socioeconomic status of the parents, past radiation exposure, family history of cancer, animal contact, maternal smoking during pregnancy, and information about where the child lived until the age of 6 years. None of these potential confounders led to a noticeable change in the risk estimates. However, little is known about the etiology of childhood brain tumors. Apart from some rare genetic factors and high doses of ionizing radiation, no other risk factors have yet been established (29,30). Nevertheless, it cannot be excluded that we missed some potentially but still unknown relevant risk factors or confounders.

Our study also has limitations. We recruited case patients during a 4-year period in four countries. We chose the age range of the participants to maximize the probability of exposure to mobile phones. Nevertheless, because childhood brain tumors are rare (30), we could eventually include only 352 case patients and about two control subjects for each patient. Thus, the statistical power of the study to detect small risk increases was limited. In addition, we carried out multiple tests and some statistically significant results can be expected by pure chance underlining our cautious interpretation of the few positive findings.

There might also be an inherent limitation regarding the level of exposure in our study. Use of mobile phones is common among adolescents and children, and it is possible that the amount of use has increased since CEFALO was carried out. For example, 8% of participants aged 12–15 years at the time of diagnosis were already regular mobile phone users at the age of 10, whereas this was true for only 2% of participants aged 16–19 years at the time of diagnosis. Notably, most participants in our study used Global System for Mobile Communication (GSM) type mobile phones, whereas use of Universal Mobile Telecommunications System (UMTS) phones is becoming more popular and widespread nowadays. Recent studies have demonstrated that the average output power

of UMTS phones is 100–500 times lower than that of a typical GSM phones during average use (31,32). Thus, the actual time-weighted exposure of the brain to radio frequency radiation may even have decreased in more recent years despite the increased use of mobile phones.

A recent study (33) that investigated the incidence of malignant and benign childhood central nervous system neoplasms in the Nordic countries found that the incidence rates of brain tumors in children aged 0–14 years remained stable at a high level during the last 22 years and concluded that major changes in environmental risk factors are unlikely. The same study, however, found a statistically significant increase in incidence of 1.02% per year for children aged 10–14 years. In England, no increase in the brain tumor incidence was observed between 1998 and 2007 among adolescents aged 10–20 years (33). Furthermore, a study that analyzed the brain cancer incidence trends in the United States reported stable time trends from 1992 to 2006 for both boys and girls who were younger than 20 years (34). These data are in line with our evaluation of time trends of brain tumor incidence in Sweden and altogether provide little support to the view that mobile phone use increases the risk of brain tumors.

In summary, we did not observe that regular use of a mobile phone increased the risk for brain tumors in children and adolescents. However, in a small subset of study participants for whom operator recorded data was available, brain tumor risk was related to the time elapsed since the start of their mobile phone subscriptions but was not related to the amount of use. The lack of an exposure–response relationship, given our finding that risk was related to neither the amount of mobile phone use and nor the location of the tumor, does not support a causal interpretation. Moreover, brain tumor incidence in Sweden has not increased among children and adolescents in the last few years. We cannot, however, rule out the possibility that mobile phones confer a small increase in risk and therefore emphasize the importance of future studies with objective exposure assessment or the use of prospectively collected exposure data. We doubt that further retrospective studies based mainly on recall will contribute to clarification. We also recommend rigorous joint efforts of population-based cancer registries to monitor time trends in incidence rates including collection of complete diagnostic data such as tumor topography, morphology, and laterality for at least the majority of patients. Because use of mobile phones has become very common among children and adolescents in most countries worldwide, even a small risk increase should be reflected in future incidence rate trends.

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5 Exposure to animals and farm life and risk of brain tumors among children and adolescents

5.1 Article 5: Brain tumors in children and adolescents and exposure to animals and farm life: a multicenter case-control study (CEFALO)

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Abbreviations

CBT: Childhood brain tumor

BT: Brain tumor

OR: Odds ratio

aOR: Adjusted odds ratio

uOR: Unadjusted odds ratio

CI: Confidence interval

PNET: Primitive neuroectodermal tumor

Abstract

Objectives: The etiology of brain tumors in children and adolescents is largely unknown, and very few environmental risk factors have been identified. The aim of this study was to examine the relationship between pre- or postnatal animal contacts or farm exposures and the risk of childhood brain tumors (CBTs), since infectious agents may pose a risk factor and a proposed mechanism is transferal of infectious agents from animals to humans.

Methods: The case-control study conducted in Denmark, Norway, Sweden and Switzerland included brain tumor cases diagnosed from 2004 to 2008 aged 7 to 19 years at diagnosis. 352 cases (83% participation rate) were matched to 646 population-based controls (71% participation rate). Conditional logistic regression was used to estimate odds ratios.

Results: Maternal farm residence during pregnancy was inversely related to all CBTs combined (adjusted odds ratio [aOR]=0.40, 95% confidence interval [CI]=0.19 to 0.88), as was the child's farm residence but not statistically significantly (aOR=0.57, 95% CI=0.28 to 1.17). Exposure to animals was in general not related to CBT risk except postnatal contact with birds showing reduced aORs of all CBTs (aOR=0.67, 95% CI=0.46 to 0.97) and PNETs (aOR=0.28, 95% CI=0.10 to 0.83). Sensitivity analyses focusing on early exposure of the child did not change the associations observed for the entire exposure period with the exception of exposure to goats and sheep which was associated with reduced risks of both all CBTs (aOR=0.48, 95% CI=0.24 to 0.97) and astrocytomas (aOR=0.29, 95% CI=0.10 to 0.87).

Conclusion: Altogether, our data indicate an inverse association between the mother during pregnancy or the child living on a farm and CBT risk, which contrasts existing literature and merits further attention. With respect to exposure to animals we did not observe any systematic pattern. This suggests that a potential protective effect of farm residence is mediated by some other factor than animal contact.

Introduction

Cancer is the second most common cause of death among children in developed countries (1). Childhood brain cancer is the second most common type of cancer in children in developed countries only surpassed by leukemia (2,3). The annual incidence rate of childhood brain tumors (CBTS) in children (0–14 years) in Europe is around 30 per million (2). Rising incidence rates have been reported over the past decades (4). However, more recent studies suggest that this rise is at least partly attributable to better diagnostic tools (MRI and CT scanners) and changes in classification practices (3).

For the majority of brain tumors the etiology is unknown, and genetic conditions such as neurofibromatosis, tuberous sclerosis, nervoid basal cell, Turcot- and Li-Fraumeni syndromes account for less than 5% of all CBTS (5,6). The only established environmental risk factor is ionizing radiation at therapeutic doses (5,6). Several other environmental factors have been suggested to play a role in the etiology of CBTS but with inconclusive results (5).

Another suggested risk factor for CBTS is exposure to infectious agents, and a proposed mechanism is transferal of infectious agents from animals to humans, thus making animal contacts a potential risk factor for CBTS. One of the suspected agents has been toxoplasma gondii, a protozoan parasite ingested by the child or by the mother and transmitted from mother to child transplacentally (7). Other suspected agents are animal viruses which have shown neurocarcinogenic effects in animals (8) and may therefore also be carcinogenic in humans (7). The immune system of young children is vulnerable during the first part of life (9) and the blood-brain barrier is not fully developed at birth (10,11), which could allow these infectious agents easier access to the brain during pregnancy and in early childhood.

Some studies have reported animal contacts to be associated with increased risk of CBTS. However, these studies focus primarily on farm animals and farm residence (12-18). The studies did not take into account other farm exposures that might partially or

fully explain the observed associations between animal exposure and CBTs. Farm related exposures could include a multitude of potentially carcinogenic factors such as: N-nitroso compounds, dust, fungi, microbes and pesticides, which are suspected to be associated with childhood cancer in general (19). Moreover several of these studies have small sample sizes, so the risk estimates have wide confidence intervals.

The present study aims to examine all types of animal contacts including pets and farm animals, while separating the effect of farm exposure. The objective of this study is to examine the association between animal- and farm exposures and the risk of CBTs in children and adolescents aged 7 to 19 years at diagnosis.

Methods

The CEFALO study is a multinational case-control study carried out in Denmark, Norway, Sweden, and Switzerland between 2004 and 2008 following a common study protocol.

Case and control ascertainment

Eligible cases were all children aged 7 to 19 years diagnosed with a primary intracranial tumor during the study period. The study period varied slightly across the participating countries (Denmark Jan 2004-Apr 2008, Sweden April 2004-August 2008, Switzerland May 2004-May 2008, and Norway Sep 2004-Aug 2008). Eligible cases had to be diagnosed with one of the following diagnoses in the International Classification of Diseases, tenth revision (ICD-10): C71, C72.9, D33.0–33.2, D33.9, D43.0–43.2, or D43.9. Tumor types were classified according to the International Classification of Childhood Cancer, version 3 (ICCC-3) (20) as follows: IIIa Ependymoma (9383, 9391–9393), IIIb Astrocytoma (9384, 9400–9401, 9410–9411, 9420–9424, 9440–9442), IIIc embryonal central nervous system (CNS) tumor/primitive neuroectodermal tumors (PNET) (9470–9474, 9480, 9502–9504, 9508), IIId other glioma (9380–9382, 9430, 9444, 9450–9451, 9460), IIIe other specified intracranial neoplasms (8743, 9064, 9071, 9080, 9161, 9390, 9412–9413, 9492–9493, 9505–9507, 9560), IIIf unspecified intracranial neoplasms (8000–8005, 9990, 9999). For the analyses the tumors were classified as: astrocytoma (astrocytomas and other gliomas), PNET (intracranial and intraspinal embryonal tumors including medulloblastoma) and all CBTS (PNET, astrocytoma, ependymoma, other specified intracranial neoplasms and unspecified intracranial neoplasms).

To attain complete case ascertainment, cases were identified both in registries and from direct reports from pediatric, oncology and neurosurgery hospital departments. Swedish and Danish cases were identified by use of a unique personal identification number through national registries (National Cancer Registry (21,22); Childhood Cancer Registry (Denmark and Sweden), Pathology Registry, The National Patient Regis-

try; Regional Cancer Registries (Sweden)) and from medical records. In Norway cases were identified through the National Cancer Registry (22) by use of a unique personal identification number and verified by the treating physicians. In Switzerland cases below 16 years of age at diagnosis were identified from the Swiss Childhood Cancer Registry. Cases between 16–19 years at the time of diagnosis were identified through neurosurgery clinics, departments of pathology and cantonal general cancer registries. All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. Date of diagnosis was defined as the date of the first conclusive diagnostic image and was established from medical records for all countries except Norway where registry data were available.

Two live controls per case were randomly selected from nationwide population registries in the Scandinavian countries. In Switzerland, a two-stage random sampling procedure was applied for the selection of control subjects in the absence of a national population registry. First, a community was randomly determined within the same language region as each patient, and second, the control subject was randomly selected from the corresponding communal population registry. Controls were individually matched by age (Denmark, Switzerland and Sweden: year and month of birth, Norway: year of birth), gender, and region. The reference date for controls was the date of diagnosis of the matched case.

Based on medical records, cases diagnosed with neurofibromatosis (von Recklinghausen's disease; 12 patients) and tuberous sclerosis were excluded (one patient). Cases and controls with severe autism, severe mental retardation or complete deafness before date of diagnosis, were excluded (two patients and two control subjects). In addition, families with insufficient language skills to complete an interview were excluded (15 patients and 36 control subjects). In Switzerland interviews were offered in German and French.

The study was approved by the national data protection boards and ethical committees in all participating countries.

Data collection

Cases diagnosed before June 2006 (Norway: December 2007) and corresponding controls were included retrospectively. All other cases were included prospectively.

Signed informed consents were given by all participants. Before contacting cases, authorization was obtained from the respective treating physician. In accordance with physicians' recommendations, parents of deceased cases were contacted at the earliest six months after the death of the child. A structured personal interview was performed with the child and one or preferably both parents by a trained interviewer using a computer assisted personal interview (CAPI) questionnaire (Denmark and Norway) or a paper version of the questionnaire (Sweden and Switzerland). In a few cases (n=9) the interview was conducted by use of computer assisted structured telephone interview or by a mailed adjusted version of the questionnaire. All families who refused to participate were asked to complete a short non-responder questionnaire, except when a written refusal was obtained in Denmark. Questionnaire translations were validated and pilot tested in all participating countries.

Exposure assessment

The animal exposure questions covered several species of animals, some animal exposures were rare (spiders), and some were relatively similar (hamster and guinea pig). In order to obtain higher statistical power in the analyses, some animal exposures were grouped.

The "cats" and "dogs" variables are only cats and dogs, as these were the most common animal exposures and no pooling was necessary. The variable "rodents" comprises the following animal exposures: rabbits, hamsters, guinea pigs, mice and rats. Bird exposure comprises exposure to chickens/turkeys/ducks and other birds. The variables pigs and cows is only exposure to those animals. Horse and pony exposure was covered by a single question and pooled with donkey exposure. Goat and sheep exposure was combined as well. The last animal exposure variable is "other animals", the

questionnaire contained a category for other animals, but several exposures were very rare and did not fit any of the other categories, hence the variable "other animals" contained the following exposures: other furry animals, other animals, fish, turtles, snakes/reptiles and insects/spiders.

Two sets of questions were asked for each animal exposure, one for contact at the home and one for contact outside the home. Further questions regarding the location of the contact were asked for cat, dog and rabbit exposure, to determine whether the animal was kept predominantly outside or inside the house. These questions regarding different levels of exposure could establish whether a dose-response effect was present and was used for sub-analyses only. The main analyses, however, focused on whether the child had contact with the specific animal or not.

For postnatal exposure a minimum of one year exposure to the animal was required to qualify as sufficiently long exposure, and exposure within two years of the reference date was discounted to exclude children with early symptoms that could lead to precautionary behavior of the parents. For prenatal animal exposure, any regular contact with animals during the pregnancy was included.

"Postnatal farm exposure" was determined as the primary residence of the child during the first six years of life. The question aimed to identify the place where the child spent the majority of his or her time during the first six years of life. The variable was analyzed as living on a farm or not living on a farm. "Prenatal farm exposure" was defined as the primary residence of the mother during pregnancy.

Confounding factors

Atopic disease was defined as the occurrence of any atopic disorder, which could be asthma or wheeze, eczema or allergic rhinitis including hay fever. "Parents' level of education" was measured as the highest obtained education of any parent, and coded as a categorical variable with three categories: high, medium and basic education.

"Childcare attendance" was defined as the child attending daycare before the age of six years, and measured as a yes/no variable.

Statistical analysis

Data were analyzed using conditional logistic regression keeping the original matching. Risk estimates were expressed as odds ratios (OR) with associated 95% confidence intervals (CI). For each analyses two models were constructed, one without additional adjustment and one adjusted with potential confounding factors selected by developing directed acyclic graphs (DAGS) for each exposure measure, and consequently different confounders were chosen for each adjusted model (23). The analyses were performed for the two most common CBT subgroups (PNETS and astrocytomas) as well as a combined CBT group. To examine whether young children are at higher risk because of an immature immune system, we performed additional sensitivity analyses focusing exposure during the first three years of life. All analyses were performed using SAS 9.2.

Results

Of the 423 eligible children 352 families chose to participate (83%). Of 909 eligible controls 646 participated resulting in a response rate of 71%. Reasons for non-participation included: parents could not be reached, parents did not wish to participate or did not have time or the child was too ill to participate.

Astrocytoma was the most common diagnosis (46%), followed by PNET (18%), other specified BTS (15%), other gliomas (8%), unspecified BTS (7%) and ependymoma (6%). The tumor types were largely distributed as expected from the existing literature (3,4,24,25), although the proportion of ependymomas was smaller, presumably due to the specific age distribution ranging from 7 to 19 years.

The distribution of cases and controls did not differ much with regard to most potential confounders and, evidently, the matching variables (Table 1). A larger proportion of control mothers lived on a farm during pregnancy. It also appeared that a larger proportion of control children lived on a farm during their first six years of life.

Table 1: Descriptive characteristics of variables of interest and potential confounders.

	Controls		CNS tumor cases	
	n	%	n	%
Age				
- 7–14	412	63.8	222	63.1
- 15–19	234	36.2	130	36.9
Sex				
- Male	353	54.6	190	54.0
- Female	293	45.4	162	46.0
Country				
- Denmark	170	26.3	85	24.2
- Sweden	228	35.3	138	39.2
- Norway	78	12.1	44	12.5
- Switzerland	170	26.3	85	24.2
Educational level of the parents*				
- Not living with parents	2	0.3	0	0.0
- Basic	26	4.0	20	5.7
- Medium	336	52.3	188	53.4
- Higher	279	43.4	144	40.9
Day care attendance				
- Daycare	557	86.2	308	87.5
- No daycare	86	13.3	44	12.5
- Unknown	3	0.5	0	0.0
Atopic disease**				
- Present	191	29.6	103	29.3
- Not present	349	54.0	191	54.3
- Unknown	106	16.4	58	16.5
Maternal place of residence during pregnancy				
- On a farm	38	5.9	9	2.6
- Not on a farm	594	92.0	341	96.9
- Unknown	14	2.2	2	0.6
Childs place of residence, first 6 years of life				
- On a farm	43	6.7	12	3.4
- Not on a farm	602	93.2	340	96.6
- Unknown	1	0.2	0	0.0

*Educational level of the highest educated parent.

**Asthma, wheeze, hay fever or eczema

The majority of odds ratios for postnatal animal exposure were below unity (Table 2); however, the confidence intervals were wide. There were few statistically significant results: postnatal exposure to birds was associated with a lower odds ratio for all BTS (aOR=0.67, 95% CI=0.46–0.97) and for PNETS (aOR=0.28, 95% CI=0.10 to 0.83). Post-

natal exposure to other animals yielded an increased risk of PNETS (aOR=4.75, 95% CI=1.83 to 12.36).

Table 2: Association between postnatal animal and farm exposure and BTS among 352 children with CBTS: unadjusted (UOR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI).

		Controls	All brain tumors					Astrocytoma					PNET				
		N (%)	N (%)	UOR	95% CI	AOR	95% CI	N (%)	UOR	95% CI	AOR	95% CI	N (%)	UOR	95% CI	AOR	95% CI
Dogs*																	
-	**Yes**	305 (48.7)	165 (48.7)	1.00	0.75-1.29	1.08	0.77-1.50	89 (48.1)	0.88	0.62-1.26	0.91	0.58-1.42	27 (44.3)	1.02	0.54-1.91	1.03	0.46-2.92
-	**No**	321 (51.3)	199 (51.3)	1	-	1	-	96 (51.9)	1	-	1	-	34 (55.7)	1	-	1	-
Cats*																	
-	**Yes**	340 (55.8)	172 (52.1)	0.87	0.66-1.14	0.81	0.58-1.13	98 (55.3)	0.89	0.62-1.28	0.89	0.56-1.44	28 (45.9)	0.78	0.41-1.49	0.90	0.42-1.91
-	**No**	269 (44.2)	158 (47.9)	1	-	1	-	79 (44.6)	1	-	1	-	33 (54.1)	1	-	1	-
Rodents*																	
-	**Yes**	293 (48.2)	145 (46.3.)	0.93	0.70-1.22	1.11	0.79-1.57	85 (48.9)	0.95	0.66-1.36	1.38	0.84-2.25	21 (40.4)	0.81	0.41-1.58	1.19	0.49-2.90
-	**No**	315 (51.8)	168 (53.7)	1	-	1	-	89 (51.1)	1	-	1	-	31 (59.6)	-	-	1	-
Birds*																	
-	**Yes**	206 (32.8)	84 (25.1)	**0.70**	0.52-0.95	**0.67**	0.46-0.97	49 (26.5)	0.78	0.53-1.16	0.82	0.50-1.36	9 (15.0)	**0.33**	0.14-0.82	**0.28**	0.10-0.83
-	**No**	423 (67.2)	251 (74.9)	1	-	1	-	136 (73.5)	1	-	1	-	51 (85.0)	1	-	1	-
Pigs*																	
-	**Yes**	41 (6.4)	20 (5.8)	0.89	0.50-1.56	0.98	0.49-1.96	8 (4.2)	0.68	0.29-1.60	0.51	0.17-1.57	5 (8.1)	1.88	0.49-7.22	2.02	0.45-9.08
-	**No**	598 (93.6)	328 (94.2)	1	-	1	-	183 (95.8	1	-	1	-	57 (91.9)	1	-	1	-
Cow*																	
-	**Yes**	60 (9.3)	21 (6.0)	0.64	0.37-1.08	0.77	0.40-1.51	10 (5.2)	0.61	0.29-1.30	0.54	0.20-1.47	5 (7.9)	1.16	0.32-4.14	1.54	0.19-12.49
-	**No**	586 (90.7)	329 (94.0)	1	-	1	-	182 (94.8)	1	-	1	-	58 (92.1)	1	-	1	-
Horse/pony/donkey*																	
-	**Yes**	82 (12.9)	45 (13.0)	1.00	0.67-1.85	1.14	0.69-1.87	20(10.6)	0.94	0.53-1.69	0.80	0.37-1.73	11 (17.7)	1.48	0.60-3.66	1.54	0.44-5.35
-	**No**	556 (87.1)	302 (87.0)	1	-	1	-	169 (89.4)	1	-	1	-	51 (82.3)	1	-	1	-
Goat/sheep*																	
-	**Yes**	38 (6.2)	14 (4.1)	0.68	0.35-1.31	0.83	0.39-1.75	5 (2.7)	0.49	0.18-1.37	0.35	0.11-1.16	2 (3.2)	0.54	0.10-2.79	0.94	0.14-6.24
-	**No**	575 (93.8)	326 (95.9)	1	-	1	-	179 (97.3)	1	-	1	-	60 (96.8)	1	-	1	-
Other animals*																	
-	**Yes**	187 (30.9)	117 (35.6)	1.09	0.80-1.49	1.33	0.92-1.91	63 (34.8)	0.91	0.60-1.37	1.10	0.66-1.83	28 (45.2)	**2.17**	1.05-4.47	**4.75**	1.83-12.36
-	**No**	419 (69.1)	212 (64.4)	1	-	1	-	118 (65.2)	1	-	1	-	34 (54.8)	1	-	1	-
Farm residence**																	
-	**Yes**	43 (6.7)	12 (3.4)	**0.47**	0.24-0,93	0.57	0.28-1.17	6 (3.1)	0.50	0.20-1,30	0.57	0.21-1.53	4 (6.4)	1.16	0.32-4.14	0.89	0.24-3.34
-	**No**	602 (93.3)	340 (96.6)	1	-	1	0	187 (96.9)	1	-	1	-	59 (93.6)	1	-	1	-

*AOR for analyses of animal exposures=adjusted for: parents' level of education, atopic disorders, place of residence and child care attendance.

**AOR for analysis of farm residence=adjusted for: parents' level of education and atopic disorders.

In the unadjusted analysis a statistically significant lower odds ratio was observed for all BTs in children living on a farm (OR=0.47, 95% CI=0.24 to 0.93). After adjusting for confounders the result was no longer statistically significant.

The maturing immune system of a young child may be more vulnerable to infectious agents. Based on this hypothesis, we reanalyzed the data with exclusion of all animal exposure occurring after the third year of life (Appendix Table 1). Exposure to cats was associated with a lower odds ratio of all BTs in the unadjusted model (OR=0.71, 95% CI=0.54 to 0.95), but not after adjustment for confounders (aOR=0.75, 95% CI=0.53 to 1.05). Exposure to goats and sheep was associated with a lower odds ratio both for all BTs (aOR=0.48, 95% CI=0.24 to 0.97) and for astrocytomas (aOR=0.29, 95% CI=0.10 to 0.87). All other results were not statistically significant and similar to the results in the analysis of the full data set.

In the analysis of prenatal exposures, i.e. the exposure of the mother during pregnancy (Table 3), most ORs were below unity indicating protective effects of prenatal exposure to animals and farm residence, but few of them were statistically significant. Exposure to cows during pregnancy yielded a statistically significantly lower odds ratio of all CBTs before adjustment (OR=0.40, 95% CI=0.18 to 0.86); after adjustment the protective effect was still present, but the result was not statistically significant. Farm residence during pregnancy was a protective factor for all CBTs both before (OR=0.40, 95% CI=0.18 to 0.86) as well as after adjustment for potential confounding factors (aOR=0.40, 95% CI=0.19 to 0.88).

Appendix table 1: Association between animal exposure during the first three years of life and BTs among 352 children with CBTs: unadjusted (UOR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI).

		Controls	All CNS tumors					Astrocytoma					PNET				
		N (%)	N (%)	UOR	95% CI	AOR	95% CI	N (%)	UOR	95% CI	AOR	95% CI	N (%)	UOR	95% CI	AOR	95% CI
Dogs																	
-	**Yes**	257 (41.1)	130 (38.4)	0.89	0.68-1.18	0.98	0.70-1.36	71 (38.4)	0.84	0.58-1.21	0.85	0.54-1.33	22 (36.1)	0.88	0.45-1.70	1.09	0.48-2.47
-	**No**	369 (58.9)	209 (61.6)	1	-	1	-	114 (61.6)	1	-	1	-	39 (63.9)	1	-	1	-
Cats																	
-	**Yes**	271 (44.5)	119 (36.1)	**0.71**	0.54-0.95	0.75	0.53-1.05	66 (37.3)	0.71	0.48-1.04	0.65	0.40-1.07	21 (34.4)	0.71	0.37-1.39	0.85	0.39-1.82
-	**No**	338 (55.5)	211 (63.9)	1	-	1	-	111 (62.7)	1	-	1	-	40 (65.6)	1	-	1	-
Rodents																	
-	**Yes**	185 (37.0)	76 (31.2)	0.73	0.50-1.06	0.75	0.48-1.17	42 (32.1)	0.86	0.53-1.40	0.89	0.48-1.64	10 (24.4)	0.83	0.33-2.10	0.90	0.28-2.89
-	**No**	315 (63.0)	168 (68.8)	1	-	1	-	89 (67.9)	1	-	1	-	31 (75.6)	1	-	1	-
Birds																	
-	**Yes**	153 (26.6)	54 (17.7)	**0.58**	0.40-0.83	**0.61**	0.39-0.94	28 (17.1)	0.62	0.38-1.01	0.65	0.35-1.21	7 (12.1)	**0.34**	0.13-0.88	**0.31**	0.09-0.99
-	**No**	423 (73.4)	251 (82.3)	1	-	1	-	136 (82.9)	1	-	1	-	51 (87.9)	1	-	1	-
Pigs																	
-	**Yes**	32 (5.1)	14 (4.1)	0.85	0.44-1.64	0.84	0.38-1.86	6 (3.2)	0.68	0.26-1.80	0.46	0.13-1.59	4 (6.6)	2.98	0.53-17.0	3.23	0.45-23.42
-	**No**	598 (94.9)	328 (95.9)	1	-	1	-	183 (96.8)	1	-	1	-	57 (93.4)	1	-	1	-
Cows																	
-	**Yes**	56 (8.7)	18 (5.2)	0.58	0.33-1.01	0.74	0.36-1.49	8 (4.2)	0.49	0.22-1.12	0.49	0.17-1.41	5 (7.9)	1.16	0.32-4.14	1.54	0.19-12.49
-	**No**	586 (91.3)	329 (94.8)	1	-	1	-	182 (95.8)	1	-	1	-	58 (92.1)	1	-	1	-
Horses/ponies/ donkeys																	
-	**Yes**	72 (11.5)	42 (12.2)	1.09	0.71-1.67	1.31	0.78-2.20	22 (11.5)	1.24	0.69-2.22	1.15	0.54-2.50	9 (15.0)	1.44	0.52-3.96	1.91	0.49-7.42
-	**No**	556 (88.5)	302 (87.8)	1	-	1	-	169 (88.5)	1	-	1	-	51 (85.0)	1	-	1	-
Goats/sheep																	
-	**Yes**	57 (9.0)	17 (5.0)	**0.53**	0.30-0.94	**0.48**	0.24-0.97	9 (4.8)	0.62	0.28-1.35	**0.29**	0.10-0.87	2 (3.2)	0.37	0.08-1.78	0.61	0.11-3.56
-	**No**	575 (91.0)	326 (95.0)	1	-	1	-	179 (95.2)	1	-	1	-	60 (96.8)	1	-	1	-
Other animals																	
-	**Yes**	116 (21.7)	67 (24.0)	1.27	0.86-1.86	1.11	0.72-1.73	37 (23.9)	1.33	0.79-2.23	1.10	0.59-2.05	18 (34.6)	**3.15**	1.25-7.90	**4.55**	1.51-13.68
-	**No**	419 (78.3)	212 (76.0)	1	-	1	-	118 (76.1)	1	-	1	-	34 (65.4)	1	-	1	-

*aOR=adjusted for: parents' level of education, atopic disorders, place of residence and child care attendance.

Table 3: Association between prenatal animal and farm exposure and BTs among 352 children with CBTs: unadjusted (uOR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI).

		Controls	All brain tumors					Astrocytoma					PNET				
		N (%)	N (%)	uOR	95% CI	aOR	95% CI	N (%)	uOR	95% CI	aOR	95% CI	N (%)	uOR	95% CI	aOR	95% CI
Dogs*																	
-	**Yes**	169 (26.2)	75 (21.3)	0.77	0.56-1.05	0.78	0.57-1.08	45 (23.3)	0.86	0.58-1.28	0.85	0.56-1.28	12 (19.1)	0.85	0.38-1.89	0.90	0.38-2.14
-	**No**	477 (73.8)	277(78.7)	1	-	1	-	148 (76.7)	1	-	1	-	51 (80.9)	1	-	1	-
Cats*																	
-	**Yes**	197 (30.5)	90 (25.6)	0.79	0.59-1.06	0.83	0.61-1.12	49 (25.4)	0.85	0.57-1.25	0.86	0.57-1.29	18 (28.6)	0.91	0.47-1.76	0.97	0.47-2.00
-	**No**	449 (69.5)	262 (74.4)	1	-	1	-	144 (74.6)	1	-	1	-	45 (71.4)	1	-	1	-
Rodents*																	
-	**Yes**	34 (5.3)	15 (4.3)	0.83	0.45-1.56	0.92	0.48-1.74	11 (5.7)	1.05	0.50-2.23	1.21	0.55-2.64	2 (3.2)	0.63	0.12-3.44	0.63	0.12-3.44
-	**No**	612 (94.7)	337 (95.7)	1	-	1	-	182 (94.3)	1	-	1	-	61 (96.8)	1	-	1	-
Birds*																	
-	**Yes**	71 (11.0)	31 (8.8)	0.77	0.49-1.20	0.83	0.53-1.31	14 (7.3)	0.59	0.32-1.11	0.64	0.34-1.21	6 (9.5)	0.76	0.27-2.18	0.76	0.26-2.23
-	**No**	575 (89.0)	321 (91.2)	1	-	1	-	179 (92.7)	1	-	1	-	57 (90.5)	1	-	1	-
Pigs*																	
-	**Yes**	21 (3.3)	8 (2.3)	0.71	0.31-1.64	1.12	0.44-2.84	4 (2.1)	0.80	0.25-2.55	1.80	0.42-7.81	3 (4.8)	1.27	0.24-6.62	1.52	0.24-9.70
-	**No**	625 (96.8)	344 (97.7)	1	-	1	-	189 (97.9)	1	-	1	-	60 (95.2)	1	-	1	-
Cow*																	
-	**Yes**	37 (5.7)	8 (2.3)	**0.40**	0.18-0.86	0.53	0.21-1.37	2 (1.0)	0.19	0.04-0.83	0.21	0.04-1.15	5 (7.9)	1.88	0.49-7.22	†	†
-	**No**	609 (94.3)	344 (97.7)	1	-	1	-	191 (99.0)	1	-	1	-	58 (92.1)	1	-	-	-
Horse/pony/donkey*																	
-	**Yes**	39 (6.0)	20 (5.7)	0.91	0.51-1.61	1.14	0.61-2.14	4 (2.1)	0.37	0.12-1.10	0.35	0.10-1.23	7 (11.1)	1.73	0.56-5.33	2.26	0.61-8.45
-	**No**	607 (94.0)	332 (94.3)	1	-	1	-	189 (97.9)	1	-	1	-	56 (88.9)	1	-	1	-
Goat/sheep*																	
-	**Yes**	21 (3.3)	5 (1.4)	0.45	0.17-1.21	0.57	0.21-1.57	3 (1.6)	0.46	0.13-1.62	0.65	0.17-2.44	1 (1.6)	2.00	0.13-31.97	2.29	0.13-41.00
-	**No**	625 (96.8)	347 (98.6)	1	-	1	-	190 (98.5)	1	-	1	-	62 (98.4)	1	-	1	-
Other animals*																	
-	**Yes**	33 (5.1)	21 (6.0)	1.18	0.68-2.04	1.19	0.68-2.07	12 (6.2)	1.58	0.73-3.44	1.74	0.78-3.89	4 (6.4)	0.79	0.24-2.59	0.80	0.24-2.65
-	**No**	613 (94.9)	331 (94.0)	1	-	1	-	181 (93.8)	1	-	1	-	59 (93.6)	1	-	1	-
Farm residence**																	
-	**Yes**	38 (5.9)	9 (2.6)	**0,40**	0,18-0,86	**0.40**	0.19-0.88	4 (2.1)	0,38	0,12-1,15	0.38	0.12-1.16	3 (4.8)	0,85	0,21-3,44	0.86	0.21-3.55
-	**No**	608 (94.1)	343 (97.4)	1	-	1	-	189 (97.9)	1	-	1	-	60 (95.2)	1	-	1	-

*aOR for analyses of animal exposures=adjusted for: parents' level of education and place of residence.

**aOR for analysis of farm residence=adjusted for: parents' level of education.

†=Not enough cases remained after adjusting to complete the analysis.

For the most common animal exposures (dogs, cats and rabbits) it was possible to assess a more detailed level of exposure. We created a cumulative measure of exposure based on whether the contact with the animal was at home or outside the home (such as at another family member's home) and if the animal was living indoors or outdoors. There was no indication of increasing ORs with increasing cumulative exposure (data not shown).

Discussion

In this study including 352 children with a BT, few statistically significant results with regard to pre- and postnatal animal contacts were found. Prenatal farm residence appeared to be a protective factor for CBTs although with respect to animal exposure the majority of the results were close to unity with confidence intervals including one. Furthermore, no major differences by tumor subgroup were identified.

Overall, the findings of this study differ from the majority of the previously published studies, discussed below in more detail. Most studies have reported at least some increased risks of CBTs associated with animal contact. Furthermore, a majority of previous studies report an increased risk of CBTs associated with farm residence. The disparities may be explained by differences in inclusion criteria, as the present study included the age group 7–19 years only, while all other studies also included children from 0 to 6 years of age. However, for the difference in age distribution to have an effect on our estimates one would expect a higher risk in younger children. One study examined the 0 to 6 year old children exclusively, and only reported statistically significant risk increases of PNETs for postnatal farm residence (12). Furthermore, the reported risk increase is comparable to that of other studies including a wider age range (13,17). Exposures were defined differently in other studies. While the present study had a wide focus which included all animal contacts, other studies have had a more narrow focus. Some studies only evaluated exposure to farm animals (14,17), some included only sick pets (18,26) and only one study had data on pets but chose to pool those with exposure to farm animals (27). Considering the numerous reports of

increased risks in the published literature, one might also consider publication bias as a possible explanation of the differences.

The finding of a protective effect of postnatal bird exposure is in contrast with the elevated risk of BTs and PNETs in children exposed to birds observed by Holly et al. (17). However, they measured poultry exposure on a farm and had no information to adjust for other farm related exposures; in addition, their confidence intervals included unity. Postnatal farm residence has been studied more often as a potential risk factor of CBTs than animal exposure. Several studies report an elevated risk of CBTs for postnatal farm residence (12-14,26). Gold et al. (84 cases, 147 controls) (26) found an increase in risk of CBTs associated with postnatal farm residence and farm animal exposure (OR=4.0, 95% CI=1.2 to 15.0); they did not define exposures further and no confounders were reported. Bunin et al. (321 cases, 321 controls) (12) observed an increased risk of PNETs (OR=5.0, 95% CI=1.1 to 46.8) but not of astrocytoma; the PNET analysis was not adjusted for confounders and postnatal farm residence was defined as ≥1 year. Cordier et al. (75 cases, 113 controls) (13) found that postnatal farm residence of at least 1 month, was associated with CBTs (OR=6.7, 95% CI=1.2 to 38.0), the analyses were adjusted for maternal age, child's age and child's sex, but based on very small numbers. Efird et al. (1218 cases, 2223 controls) (14) found an increased risk for early life farm exposure, defined as exposure before six months of age (OR=1.6, 95% CI=1.1 to 2.2), adjusted for the child's age, sex and centre. The present study showed no statistically significant results, and the ORs tended, in contrast to former studies, to be decreased, suggesting a protective effect.

The results in this study also differ from earlier literature regarding exposure during pregnancy. Farm residence during pregnancy appeared to be a protective factor for BTs in this study, while previous studies have reported it to be a risk factor (14,17). Holly et al. (540 cases, 801 controls) (17) reported elevated ORs of CBTs for maternal residence or work of one month during pregnancy (OR=1.6, 95% CI=0.86 to 2.9), the results were statistically significant if the farms held pigs (OR=3.8, 95% CI=1.2 to 12) or horses (OR=2.2, 95% CI=1.0 to 4.8). Efird et al. (14) utilized an identical definition of

farm exposure and reported increased ORs for CBTs in general (OR=1.3, 95% CI=1.0 to 1.8) but not for any tumor subgroups. Furthermore our analysis yielded null findings for all prenatal animal exposures, tending towards an inverse association for almost all animal groups. Earlier studies examining prenatal exposure to farm animals reported various positive associations with CBTs (14,17), while studies with a broader definition of animal exposure found no consistent associations (12,13,15,28), suggesting that other factors than animal exposure, related to farms, might be the risk factor.

The inverse association observed with farm residence is difficult to interpret, as farm residence might be correlated with various potential exposures, including pesticides, animal contacts, dust, viruses and microbes. An inverse association between farm residence and atopic diseases has been attributed to better training of the immune system due to stimulus by increased contact to non-pathogenic microbes (29), also known as the hygiene hypothesis. A better trained immune system may also be protective in the development of other diseases including CBTs, but this has not been previously reported.

Our study included a well-defined study population, using nationwide complete cancer registries complemented with active case searches in the respective clinics, and the controls were selected at random from nationwide population registers, and therefore sampling bias is unlikely. The response rates were high, above 80% for cases and above 70% for controls. It is not likely that the studied associations would differ for participants and non-participants. The study was one of the largest of its kind with 352 cases. An additional strength of the present study was that study subjects were blinded regarding the hypotheses of the study and trained interviewers conducted all the interviews, reducing the potential for recall or information bias.

The study also has limitations. Possibility of recall bias cannot be excluded in a retrospective study such as this, leading to differential exposure misclassification, which can either exaggerate or underestimate the effect of an exposure (30). However, a link between exposure to animals and CBTs is not prominently discussed in the public and

thus there is little reason why case families should systematically report animal or farm contacts differently compared to control families. The possibility of residual confounding also remains an issue since not all possible confounders could be adjusted for, mainly because of the unknown etiology of CBTs. However, substantial confounding seems unlikely as no strong environmental risk factors for CBTs are known.

In conclusion, this study adds to the overall uncertainty regarding animal and farm exposure and their association to CBT risk, with results showing mostly no associations or rather decreased risks contradicting the results of some previous studies. Further research on the subject should focus on finding better direct measures of exposure. A relevant measure could be infections; however most of the suspected infectious agents lead to subclinical infections, making exposure hard to assess. The observed inverse association with farm residence and the possible role of the hygiene hypothesis in the development of CBTs warrants further attention.

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6 Infectious diseases, social contact and risk of brain tumors among children and adolescents

6.1 Article 6: Patterns of infectious disease and social contact in early life and brain tumours in children and adolescents: An international case-control study (CEFALO)

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This article has been prepared for submission.

Abstract

Background: Patterns of infectious diseases and exposure to social contacts early in life have been proposed to modulate the risk of brain tumours during late childhood and adolescence.

Methods: CEFALO is an interview-based case-control study conducted in Denmark, Norway, Sweden and Switzerland including children and adolescents aged 7–19 years with a primary intracranial brain tumour diagnosed between 2004 and 2008. For each case two population controls matched on sex, birth year, and region were randomly sampled.

Results: The study included 352 cases (participation rate: 83%) and 646 controls (71%). There was no association with various measures of social contacts, including day care attendance, number of child-hours at day care, attending baby groups in first year of life, birth order, or living with other children. More frequent sick days with infections in the first six years of life were observed among cases compared to controls.

Interpretation: There was little support for the hypothesis that social contacts influence the risk of childhood and adolescent brain tumour (CABT). The association between reported sick days due to infections and risk of CABT may reflect involvement of immune functions, recall bias or, less likely, inverse causality.

Introduction

Brain tumours are the second most frequent type of childhood cancer with a high mortality rate and a high frequency of long-term morbidity and psychosocial sequlae [Reimers et al., 2003]. The annual incidence rates range from 20–40 cases per million children with the highest rates reported in the Nordic countries [Lannering et al., 2009; Peris-Bonet et al., 2006; Schmidt et al., 2011]. Better knowledge of the aetiology of childhood brain tumours (CBT) for primary prevention strategies is therefore important.

A review by Schüz et al (2002) suggests that infections could initiate or modify the risk of CBT similar to the infection hypothesis that has been demonstrated for childhood acute lymphoblastic leukaemia. The Infection hypothesis associated with childhood leukaemia [Kamper-Jorgensen et al., 2008; Roman et al., 2007; Schuz et al., 1999] suggests that lack of exposure to infectious agents early in childhood could cause an abnormal immune response when exposed to infectious diseases later in childhood which could then lead to leukaemia [Greaves, 2006]. Also Kinlen suggested leukaemia could be caused by the immune system response to an as yet unidentified infectious agent. Such infections would be more likely to happen in the situations of population-mixing [Kinlen, 1995].

For CBT the majority of studies have not found an association between infectious agents and CBTS [Birch et al., 1990; Little, 1999; McKinney et al., 1999]. Many of these studies, however, had small sample sizes and therefore low statistical power to detect an association.

A few studies, however, have found an association between risk of CBT and various measures of infectious diseases [Dickinson et al., 2002; Linet et al., 1996; Shaw et al., 2006] or indications of an association with exposure to polyoma viruses (SV40, JCV, BKV) [Bunin, 2000; Vilchez and Butel, 2003; Khalili et al., 2003]. A British study identified space-time clustering for subgroups of CBT supporting the possibility that infectious agents could influence the development of CBT [McNally et al., 2002]. Further-

more for subgroups of CNS tumours a correlation with seasonality of birth has been reported [Hoffman et al., 2007; McNally et al., 2002; Schmidt et al., 2009; Heuch et al., 1998; Feltbower et al., 2001; Brenner et al., 2004; Halperin et al., 2004; Koch et al., 2006; Mainio et al., 2006] indicating an influence of seasonal variations in community infectious diseases at time of births [Schmidt et al., 2009]. This finding has however not been supported by other studies [Choi et al., 1977; Feltbower et al., 2001; Halperin et al., 2004; Schmidt et al., 2010a].

Children's exposure to infectious diseases in early childhood is most commonly through contact with other children [Ma et al., 2009]. Studies have shown that attending daycare increases a child's risk of getting infectious diseases [Kamper-Jorgensen et al., 2006; Thrane et al., 2001; von Linstow et al., 2008] indicating that social contacts could reflect the general exposure to infections. Studies investigating the relationship between social contacts and CBT have however only found little or no evidence of an association [Harding et al., 2009; Schmidt et al., 2010; Shaw et al., 2006].

To evaluate the infection hypothesis for CBT, we investigated the patterns of infectious diseases and social contacts in early life in relation to risk of developing a brain tumour during late childhood and adolescence.

Methods

The CEFALO study is a multinational case-control study carried out in Denmark, Norway, Sweden, and Switzerland with the primary goal to investigate the possible association between CBT risk and mobile phone use and other relevant exposures [Aydin et al., 2011].

Case and control ascertainment

Eligible cases were all children diagnosed with a primary intracranial brain tumour [Aydin et al., 2011] aged 7 to 19 years at date of diagnosis. The study period was from January 1, 2004 until August 1, 2008 but varied slightly across the four countries (Denmark January 2004–April 2008, Sweden April 2004–August 2008, Switzerland May 2004–May 2008, Norway September 2004-August 2008).

To attain complete case ascertainment, cases were identified both at hospitals and in country specific disease registries (the Danish National Cancer Registry [Storm et al., 1997; Tulinius et al., 1992]; Danish Childhood Cancer Registry, Danish Pathology Registry, Danish National Patient Registry, the Swedish Regional Cancer Registries [Barlow et al., 2009], the Cancer Registry of Norway [Larsen et al., 2009] and Swiss Childhood Cancer Registry). Date of diagnosis was defined as date of first diagnostic image.

Two controls per case were randomly selected from nationwide population registries in Scandinavia and in Switzerland from communal registries, and were individually matched by age (Denmark, Switzerland and Sweden: month of birth, Norway: year of birth), gender, and region. The reference date for controls was set as date of diagnosis of matched case.

Subjects diagnosed with neurofibromatosis (von Recklinghausen, N=12) and tuberous sclerosis (TSC, N=1) were excluded. Cases and controls with severe autism, severe mental retardation or complete deafness before date of diagnosis were also excluded (N=4). In addition, families with insufficient language skills to complete an interview

were excluded (N=51). The study was approved by the National data protection boards and ethical committees in all participating countries.

Cases diagnosed before June 2006 (Norway: December 2007) and corresponding controls were included retrospectively. All other cases were included prospectively. A structured personal interview was performed with the child and one or preferably both parents by a trained interviewer at least six months after date of diagnosis during the time period 2006 to 2009. Questionnaire translations were validated and pilot tested in all participating countries.

Variables and statistical analysis

We used the following variables as measures of social contacts and of exposure to infectious disease: living with other children before age six of index child (yes/no), birth order (1st born/>1st born), attending daycare in first year of life (yes/no) and before age six (yes/no), attending baby groups within the first year of life (yes/no), mean number of days per month where child's general condition was appreciably affected by infectious disease in the first one, three, and six years of life (categorical: once or less per month, 2–3 days per month, 4 days or more per month). The infectious diseases included: cold, fever without known cause, middle ear infection, tonsillitis, bronchitis, pneumonia, infection of the skin, urinary tract infections, stomach flu, and others (e.g. whooping cough, 3 day fever, scarlet fever). For each child we also assessed cumulative daycare exposure by calculating total daycare childhours (categorized into tertiles) during the first one and six years of life as used by Ma et al (2002): Number of months attending a specific daycare × 4.35 (average number of weeks per month) × hours per week at daycare × number of children at daycare [Ma et al., 2002]. The childhours were cumulated over all daycare facilities attended during the time period of interest. As early brain tumour-related symptoms might have influenced daycare attendance, all daycare information for the last two years before diagnosis or reference date were disregarded (only relevant for the 7 and 8 year olds in our study).

For analysis tumours were classified as: “Glioma” (astrocytomas, other gliomas), “intracranial embryonal tumours” (including primitive neuroectodermal tumors [PNET]), “Others” (ependymoma, other specified intracranial neoplasms, unspecified intracranial neoplasms).

Data were analyzed by conditional logistic regression in SAS (version 9.2). Relative risk estimates were expressed as odds ratios (OR) with associated 95% confidence intervals (95% CI). Highest attained education of parents as a proxy for socio-economic status was included in the models as potential confounder, but did not alter the risk estimates and was therefore omitted from the final model (data not shown).

Results

In total, we invited 423 brain tumour cases and 909 controls and their families to participate in the CEFALO study. We interviewed 352 cases and 646 controls with participation rates of 83% and 71% respectively. The most common reasons for non-participation are shown in Table 1.

The largest group of CBT in the study was glioma (55%) followed by "other tumours" (28%) and intracranial embryonal tumours/PNET (18%) (Table 1). This corresponds with the overall distribution of tumour types in the Nordic countries [Schmidt et al., 2011].

Overall there were slightly more boys than girls in the study. Two thirds of the participating children and adolescents were between age 7–14 years while only one third was between 15 and 19 years (Table 1). A large proportion of children attended daycare before 6 years of age (87%). The majority of children attended baby groups (72%) and most of the index children were living together with siblings or other children (94%). Regarding monthly number of days with infectious disease during the first six years of life, the majority of children were reported to have infectious disease once or less per month (67%), 20% 2–3 days per month and 9% 4 days or more per month.

Table 1: Characteristics of cases and controls.

	Case (%)	Control (%)	Total (%)
No. of participants	352	646	998
Reasons for not participating			
Refusals	18 (25)	172 (65)	190 (57)
No contact could be established	5 (7)	70 (27)	75 (22)
No approval from treating physician to contact case family	19 (27)	-	19 (6)
Time shortage - study stopped before consent was received	14 (20)	-	14 (4)
Other reasons	15 (21)	21 (8)	36 (11)
Gender			
Boys	190 (54)	353 (55)	543 (54)
Girls	162 (46)	293 (45)	455 (46)
Age-group (at reference date)			
7–9	88 (25)	167 (26)	255 (26)
10–14	144 (41)	265 (41)	409 (41)
15–19	120 (34)	214 (33)	334 (33)
SES educational level			
Basic	20 (6)	26 (4)	46 (5)
Medium	188 (53)	336 (52)	524 (53)
High	144 (41)	279 (43)	423 (42)
Not living with parents	-	2 (½)	-
Missing	-	3 (½)	-
Type of tumour (ICCC groups)			
Gliomas	192		
Astrocytomas (IIIb)	162 (46)	-	
Other gliomas (IIId)	30 (9)	-	
Intracranial embryonal CNS tumours/PNET (IIIc)	62 (18)	-	
Other	98	-	
Ependymoma (IIIa)	21 (6)	-	
Other specified intracranial neoplasms (IIIe)	53 (15)	-	
Unspecified intracranial neoplasms (IIIf)	24 (7)	-	

Abbrevations: SES=Socio-economic status, ICCC=International Classification of Childhood Cancer, PNET=primitive neuroectodermal tumour.

Overall, no OR of any measure of social contacts was statistically significantly increased or decreased (Table 2); this did not change when stratifying by gender (data not shown). However, a tendency of slightly, but non-significantly, increased risks were found for glioma and total childhours (OR for highest tertile=1.76, 95% CI=0.92 to 3.38), living with other children before age six years (OR=1.64, 95% CI=0.73 to 3.67) and attending baby groups during the first year of life (OR=1.47, 95% CI=0.95 to 2.28). Such a pattern was not observed for embryonal or other CBT. Subdivision of the highest tertile of total daycare childhours indicated no dose-response effect for glioma (Table 2).

Table 2: Associations of attending daycare within 1st and 6 years of life, total daycare childhours within 6 years of life, living with other children, birth order, and attending baby groups within 1st year and Childhood brain tumour (CBT).

	Overall CBT				Glioma				Embryonal CNS tumour				Other CBT			
	Cases	Control	OR	95% CI	Cases	Control	OR	95% CI	Cases	Control	OR	95% CI	Cases	Control	OR	95% CI
Daycare within 1st year of life																
Yes	94	167	**1.11**	0.80-1.55	50	93	**1.02**	0.65-1.60	18	33	**1.17**	0.54-2.53	26	41	**1.28**	0.68-2.40
No	258	476	-		142	254	-		44	86	-		72	136	-	
Attending daycare beween 0-6 years																
Yes	308	556	**0.97**	0.63-1.49	168	299	**0.96**	0.53-1.73	55	106	**1.05**	0.36-3.05	85	151	**0.94**	0.43-2.03
No	44	87	-		24	48	-		7	13	-		13	26	-	
Total daycare childhours																
Highest tertile	115	197	**1.08**	0.69-1.70	71	97	**1.76**	0.92-3.38	13	39	**0.78**	0.23-2.63	31	61	**0.65**	0.31-1.37
Intermediate tertile	104	189	**0.97**	0.63-1.50	48	101	**1.00**	0.53-1.91	26	31	**2.14**	0.68-6.76	30	57	**0.65**	0.32-1.34
Lowest tertile	107	201	-		54	111	-		17	36	-		36	54	-	
Total daycare childhours																
Highest tertile - upper half	46	109	**0.77**	0.46-1.30	27	55	**1.14**	0.54-2.40	3	23	**0.24**	0.04-1.38				
Highest tertile - lower half	69	88	**1.46**	0.88-2.41	44	42	**2.71**	1.29-5.72	10	16	**1.54**	0.40-5.89				
Intermediate tertile	104	189	**0.97**	0.63-1.50	48	101	**1.01**	0.53-1.94	26	31	**2.28**	0.70-7.41				
Lowest tertile	107	201	-		54	111	-		17	36	-					
Living with other children before age 6																
Yes	335	601	**1.38**	0.73-2.59	182	319	**1.64**	0.73-3.67	59	110	**1.58**	0.29-8.58	94	172	**0.78**	0.22-2.78
No	15	37	-		9	25	-		2	6	-		4	6	-	
Birth order																
> 1st born	207	391	**0.89**	0.68-1.16	113	212	**0.90**	0.63-1.29	31	73	**0.63**	0.34-1.16	63	106	**1.14**	0.67-1.95
1st born	144	249	-		79	134	-		31	46	-		34	69	-	
Attending baby groups witin 1st year																
Yes	261	455	**1.12**	0.82-1.54	146	237	**1.47**	0.95-2.28	43	82	**1.00**	0.47-2.13	72	136	**0.74**	0.42-1.32
No	90	182	-		46	107	-		19	37	-		25	38	-	

Abbrevations: CBT=childhood brain tumour, OR=odds ratio, 95% CI=95%-Confidence intervals, CNS=central nervous system. Conditional logistic regression analyses, which adjusts for matching factors (age, gender, and region) expressed as odds ratio values (OR) and with 95% conficence intervals (95% CI).

For all tumour types the OR was 1.23 (95% CI=0.87 to 1.73) for children having 2-3 sick days per month in the age 0-6 years and 1.91 (95% CI=1.22 to 3.01) for children with 4 or more sick days per month (0–6 years) compared to children with one sick day or less per month (Table 3). When stratifying by gender girls tended to have higher risk estimates of CBT than boys (data not shown). In general, the risk increase was most pronounced for gliomas. For embryonal CNS tumours a risk increase was found for children with 4 or more sick days per month; however this was based on small numbers and only for the highest number of days of infectious disease. For other CBTS no indication of a risk increase with self-reported number of sick days was observed (Table 3). Regarding age of exposure, risk estimates were similar for number of sick days at the age below 1 year, 1–3 years and 3–6 years.

We tested for interaction between total daycare childhours and number of days of infections (0–<6 years) as well as for birth order and number of days of infections (0–<6 years), but no interactions were found.

Table 3: Patterns of infections measured as self-reported number of days of infectious disease and childhood brain tumour (CBT).

	Overall CBT				Gliomas				Embryonal CNS Tumor				Other CBT			
	Cases	Control	OR	95% CI	Cases	Control	OR	95% CI	Cases	Control	OR	95% CI	Cases	Control	OR	95% CI
No. of days of infectious disease (0–<1 year)																
4 days or more per month	32	39	**1.60**	0.96-2.65	23	21	**2.37**	1.22-4.63	5	6	**1.75**	0.52-5.88	4	12	**0.53**	0.16-1.74
2–3 days per month	67	122	**1.02**	0.72-1.43	35	62	**1.13**	0.69-1.82	16	27	**1.16**	0.57-2.39	16	33	**0.79**	0.41-1.52
Once or less per month	244	440	-		131	245	-		37	73	-		76	122	-	
No. of days of infectious disease (1–<3 years)																
4 days or more per month	49	61	**1.60**	1.07-2.40	32	29	**2.43**	1.39-4.24	10	10	**1.90**	0.75-4.82	7	22	**0.56**	0.23-1.37
2-3 days per month	81	131	**1.23**	0.88-1.72	45	68	**1.41**	0.88-2.26	15	33	**0.91**	0.43-1.95	21	30	**1.24**	0.67-2.28
Once or less per month	214	418	-		111	235	-		35	68	-		68	115	-	
No. of days of infectious disease (3–<6 years)																
4 days or more per month	37	43	**1.62**	1.00-2.63	25	18	**2.87**	1.45-5.67	7	7	**2.08**	0.64-6.70	5	18	**0.43**	0.15-1.25
2–3 days per month	72	144	**0.93**	0.66-1.32	39	77	**1.03**	0.65-1.65	17	34	**1.06**	0.46-2.45	16	33	**0.76**	0.39-1.49
Once or less per month	237	429	-		126	242	-		36	70	-		75	117	-	
No. of days of infectious disease (0-<6 years)																
4 days or more per month	44	46	**1.91**	1.22-3.01	29	25	**2.80**	1.52-5.16	9	6	**2.89**	1.00-8.33	6	15	**0.55**	0.19-1.58
2–3 days per month	74	122	**1.23**	0.87-1.73	42	57	**1.68**	1.03-2.74	15	27	**1.20**	0.56-2.60	17	38	**0.78**	0.42-1.47
Once or less per month	223	429	-		116	244	-		34	72	-		73	113	-	

Abbreviations: CBT=childhood brain tumour, OR=odds ratio, 95% CI=95%-Confidence intervals, CNS=central nervous system. Conditional logistic regression analyses, which adjusts for matching factors (age, gender, and region) expressed as odds ratio values (OR) and with 95% confidence intervals (95% CI).

Discussion

Overall, we found little evidence for an association between early-life social contacts and CBT risk. There was no evidence of a dose-response effect of higher CBT risk for cumulative childhours of attending daycare facilities. In all, confidence intervals for all social contact measures were wide and no systematic patterns were observed.

However, we found some evidence for an association between number of sick days due to infectious disease and CBT risk. When subdividing by tumour type, the effect was restricted to glioma with the results showing statistically significant positive associations for all age intervals.

Our findings of no increased CBT risk in relation to social contacts are broadly consistent with earlier studies, which showed only small or no associations [Harding et al., 2009; Schmidt et al., 2010; Shaw et al., 2006].

The overall association of CBT with sick days because of infections found in this study is in agreement with several other studies, however, the majority of studies did not find an association [Little, 1999] nor has a specific infectious agent been identified [Schuz and Kaatsch, 2002]. A Swedish nested case-control study based on 570 cases and 2,850 controls by Linet et al (1996) found a twofold significantly increased risk of CBT for unspecified neonatal infectious diseases [Linet et al., 1996]. Also another case-control study by Shaw et al (2006) including 272 cases and 272 controls found slightly elevated risks for CBT with use of antibiotics in childhood [Shaw et al., 2006], though statistically not significant. An ecological study in the UK found elevated risks of CBT for postnatal exposure to high community levels of measles (OR=2.1, 95% CI=1.3 to 3.6) and influenza (OR=3.3, 95% CI=1.5 to 7.4) [Dickinson et al., 2002]. However, this association was not confirmed in a later study based on a larger data set including the initial population [Nyari et al., 2003].

Estimates of sick days because of infections were based on self-reported information listing the frequency of infections in the first six years of the child's life (infectious calendar developed for the purpose of this study, see online appendix). This measure could introduce several problems as recollection of infections is difficult [Schmidt et al., 2010] and self-reported information, in this case given by laypersons, introduces uncertainty regarding the diagnoses of infectious diseases. The association between number of sick days and risk of CBT can be influenced by recall bias. On one hand case mothers would likely seek an explanation or reason for their child's diagnosis, thus over-reporting the frequency of infectious diseases compared to control mothers. On the other hand case mothers could tend to under-report infectious diseases as these do not seem important in comparison with a CBT diagnosis, making infectious diseases less likely to be remembered by case mothers. For control mothers common infectious diseases could be ascribed as more serious, leading to better recollection and consequently reported more often.

If differential recall bias was present in this study, we would expect to find the same effect for all subtypes of CBT; however, we see elevated risk estimates for gliomas but not for embryonal CNS tumours and the group of "other" CBTS, possibly indicating that the bias for reporting of infectious diseases is not very strong. However, the groups of embryonal CNS tumours and other CBTS are small and the difference may be due to random variation.

Furthermore it is possible that birth order could influence the reporting of infectious disease as mothers tend to have a more accurate recollection of the first years of the first born child compared to later born [Sou et al., 2006]. We found no evidence for this possible reporting error in our results as no interaction between birth order and number of sick days was observed.

When interpreting these results it is important to keep in mind that the measure of infectious diseases in this study is reported by laypersons. If case parents not only report infectious diseases but in addition mistakenly interpret prodromal symptoms

of the brain tumour as infectious disease, this would place cases in the higher exposure groups. Some of the most common symptoms of CBT are headache, nausea and vomiting and many initial signs of CBT also resemble more common and less serious illnesses [Wilne et al., 2007]. Furthermore it has been established that doctor's and patient's delay is a problem in childhood malignancies [ng-Tan and Franco, 2007; ng-Tan et al., 2008; Raab and Gartner, Jr., 2009; Wilne et al., 2007] with some delays having a maximum of 12 years [Raaschou-Nielsen et al., 2006] thereby making it more likely that reported infections of cases could reflect prodromal symptoms. In order to avoid such potential influence on the results of this study, exposure occurring within two years before diagnosis was excluded. We cannot, however, rule out that diagnostic delay might still influence the results.

Diagnostic delay may also play a role by possibly introducing confounding by indication to the social contacts analyses, as cases might attend daycare less often compared to controls due to prodromal symptoms or other factors relating to a latent and undiagnosed CBT. This could lead to an underestimation of the association between social contact and the risk of CBT.

Based on the results of this study and taking previous studies into account, we consider it possible that general infectious diseases or specific infectious agents modulate the risk of subgroups of CBT. Another possibility is that immunological factors in cases influence the risk of developing a tumour as well as increase the susceptibility to infectious diseases.

One of the strengths of this study is the high participation rate, reducing the potential of selection bias. Use of nationwide and high quality registries [Storm et al., 1997; Tulinius et al., 1992; Barlow et al., 2009] in addition to case validation from treating physicians in hospitals ensures a complete case ascertainment. Furthermore cases were validated by unequivocal diagnostic imaging or histological confirmation ensuring correct diagnoses of included cases. The complete Nordic and Swiss population registers provided an optimal sampling frame for population-based controls.

In our study the majority of children in all countries (63–97%) attended daycare making it a substantial source of social contacts with other children and therefore also for repeated contact with infectious agents. This in combination with a range of other measures of social contacts and infectious diseases, allowed us to establish a quite detailed picture of the children's total exposure. Information on siblings and other children living in the same household before age six of index child allows for an important improvement in this study compared to previous studies lacking this detailed information [Altieri et al., 2006; Emerson et al., 1991; Heuch et al., 1998; Linet et al., 1996; Mogren et al., 2003; Schmidt et al., 2010; Shaw et al., 2006; Von and Reynolds, 2003]. This was even more important when taking the nature of modern family structures into account, namely accounting for stepbrothers and stepsisters or any children of new partners of one of their parents.

With such a generally high proportion of children attending daycare, it became difficult to investigate daycare as a risk factor; However, we created the score of childhours at daycare as exposure gradient and did not observe an association with CBT risk when comparing children of the highest and lowest tertile of childhours at daycare.

Whereas interview information about birth order and living with other children is expected to be accurate, information on daycare attendance may be difficult to recollect many years later. We believe, in contrast to the reported infectious diseases, that it is unlikely that case and control parents remember daycare attendance differently. Thus there is the possibility that non-differential bias could influence the risk estimates possibly leading to an underestimation of the association.

In conclusion, this study provides little evidence of an association between increased social contacts in early life as measured by daycare attendance, participation in baby groups, or living together with other children, and the risk of CBT in 7–19 year olds. However, we observed more frequent reported sick days because of infections in the first six years of life associated with the risk of glioma and possibly embryonal brain tumour. The association for gliomas needs to be further studied to identify whether

infectious disease early in life represent early symptoms of CBT, have the same underlying cause as CBT or modulate the risk of developing a CBT.

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7 Summary of the main findings

This section contains a short summary of the thesis according to the aims outlined in chapter 2.2 on page 67. The detailed findings can be found in the respective articles.

Aim 1: Assess how recall errors and selection bias influence the risk estimates in case-control studies about mobile phone use and brain tumors in children and adolescents.

In the validation study, case patients overestimated their cumulative number of calls by 9% on average (interquartile range [IQR]=−53% to 127%) and controls by 34% (IQR=−37% to 436%). Case patients also overestimated their cumulative duration of calls by 52% on average (IQR=−30% to 328%) and controls by 163% (IQR=−11% to 906%). The random recall errors were substantial. There was little evidence that the median overestimation of cumulative number of calls differed between case patients and control subjects (Mann-Whitney *U*-test, p=0.20). Borderline significant evidence was found that overestimation of duration of calls was more pronounced among control subjects than in case patients (p=0.07).

The observed odds ratio for regular use increased with increasing random recall errors of controls and decreased with increasing random recall errors of cases (independently from the true OR). The opposite pattern was found for heavy users for the no-risk scenario (OR=1). A more complex pattern was observed for the heavy users in the scenario where we assumed that the true OR was 1.5.

The observed odds ratio for regular use of mobile phones increased with increasing systematic recall errors of cases and decreased with increasing systematic recall errors of controls. This was also true for heavy use of phones. Whenever cases had higher systematic recall errors than controls, we observed overestimated ORs for regular and heavy use. The opposite was true whenever controls had higher systematic recall errors than cases. This was true for both a true OR of 1 and 1.5.

When we combined random and systematic recall errors, the biased effects of systematic recall errors were shifted towards unity with increasing random recall errors. The finding that the effects of systematic recall errors were attenuated by the random recall errors were independent of the true assumed risk of mobile phones.

The simulated OR for regular and heavy use of mobile phones underestimated the true risk estimate in the scenarios in which unexposed controls (non-users of mobile phones) or exposed cases (mobile phone users) were under-represented. The opposite was true when unexposed cases were under-represented.

Almost no bias in the odds ratio for regular use was observed in all plausible scenarios for CEFALO. However, we observed downward biased ORs for heavy use in all scenarios when a true risk of mobile phones was assumed.

Aim 2: Determine factors that predict the level and the overestimation of mobile phone use among children and adolescents.

Operator data about number and duration of calls were obtained from 48 case patients and 87 control subjects. In addition, information about time since first subscription was available from 36 Swiss case patients and 65 control subjects. The Spearman's correlation coefficient between self-reported and operator-recorded number of calls was 0.57 (95% CI=0.44 to 0.67) and 0.93 (95% CI=0.91 to 0.94) when we included those participants who stated never using a mobile phone. The Spearman's correlation co-

efficient for duration of calls was 0.57 (95% CI=0.46 to 0.68) and 0.93 (95% CI=0.92 to 0.94) when we included those participants who stated never using a mobile phone. For the time since first subscriptions, the Spearman's correlation coefficient was 0.41 (95% CI=0.30 to 0.51) and 0.94 (95% CI=0.93 to 0.95) when we included those participants who stated never using a mobile phone.

Participants of Sweden had statistically significantly less average number of calls per day (−61%) compared to participants from Denmark. No other factors were found to be statistically significantly related with frequency and amount of mobile phone use per day. Male participants tended to have a lower average number and duration of calls per day than female participants. Per year of age, average number and duration of calls per day increased by 7%, although not statistically significant.

Participants of CEFALO aged 15–19 years had a significantly higher likelihood of overestimating their cumulative number and duration of calls compared to participants aged 7–14 years. Female participants were more likely to overestimate duration of calls than male participants. A higher amount of operator-recorded mobile phone use was associated with a lower probability of overestimating the mobile phone use. Notably, no evidence was found that cases had a higher likelihood of overestimating their mobile phone use compared to controls, rather the opposite.

Aim 3: Evaluate if mobile phone use is related to brain tumor risk in children and adolescents.

We identified 423 case patients and 909 potential control subjects during the study period (2004–2008). Interviews were completed with 352 (83.2%) eligible case patients and 646 (71.1%) eligible control subjects. There were 265 (75.3%) case patients and 466 (72.1%) control subjects who reported having spoken on a mobile phone more than 20 times before the time when the case patient was diagnosed. Regular mobile phone use was reported by 194 (55%) case patients and 329 (51%) control subjects.

Regular users of mobile phones were not statistically significantly more likely to have been diagnosed with brain tumors compared with non-regular users (OR=1.36, 95% CI=0.92 to 2.02). We observed somewhat elevated odds ratios without a clear exposure-response relationship for the following exposure variables: time since first use (p_{trend}=0.37), cumulative duration of subscriptions (p_{trend}=0.14), cumulative duration of calls (p_{trend}=0.42), and cumulative number of calls (p_{trend}=0.58). Children who started to use mobile phones at least 5 years before diagnosis were not at increased risk compared with those who had never regularly used mobile phones (OR=1.26, 95% CI=0.70 to 2.28).

We found no elevated risk among regular users of mobile phones when we looked at the parts of the brain with the highest radio frequency exposure (i.e. temporal and frontal lobes and the cerebellum). A statistically significant odds ratio was found, however, for tumors in the parts of the brain with the lowest exposure to radiation among regular users of mobile phones (OR=1.92, 95% CI=1.07 to 3.44).

For the study participants for whom operator-recorded data were available, we found a statistically significantly increased risk among users with more than 2.8 years since the start of the first subscription (OR=2.15, 95% CI=1.07 to 4.29, p_{trend}=0.001). We found, however, no significant exposure-response relationships for operator-recorded cumulative duration of subscriptions, cumulative hours of use, and cumulative number of calls.

The absorbance of radiation from mobile phones is highly localized to the side of the head where the phone is held. The use of the mobile phone on the same side where the tumor occurred is called ipsilateral use whereas use of the mobile phone on the opposite side where the tumor occurred is called contralateral use. The odds ratio for brain tumor risk among ipsilateral regular users of mobile phones was not higher than the odds ratio of contralateral regular users (OR=1.74, 95% CI=0.91 to 3.33 and OR=2.07, 95% CI=0.95 to 4.52, respectively).

We found no evidence for a relationship between ever use of baby monitors near the head and brain tumor risk (OR=0.96, 95% CI=0.50 to 1.86). Furthermore, children's use of cordless phones was not related to brain tumor risk for the group with the highest amount of cordless phone use (>70 hours; OR=1.18, 95% CI=0.65 to 2.14).

A risk estimate of 2.15 after 3 years of regular mobile phone use is expected to increase the incidence rate by about 50% in the last 10 years based on the proportion of regular users in our study collective. No such trend was observed (rather the opposite) in the incidence trends among Swedish children and adolescents aged 5–19 years from 1990 to 2008. This indicates that short-term use of mobile phones does not cause brain tumors in children and adolescents.

8 General discussion

In the following section, the results of the articles are discussed in the light of the available scientific literature and their implications for further research are examined.

8.1 Recall of mobile phone use in case-control studies

Most validation studies that compared self-reported mobile phone use with objective data were conducted among adults.[57,164-168,340] Only few studies have been conducted among children and adolescents so far.[112,162,163] All studies show rather consistently that recall of past mobile phone use is afflicted with large random errors, even if the recall period is as short as six months.[166] It has to be noted that the studies differed with respect to the length of the time period from which the study participants had to recall their phone use (ranging from 1 week to ≥10 years). Systematic recall errors were found to be moderate. Correlation coefficients between self-reported and objectively measured number of mobile phone calls ranged from 0.48[167] to 0.69[166] among adults. Correlation coefficients between self-reported and objectively measured duration of mobile phone calls ranged from 0.34[164] to 0.69[166,340] among adults. In contrast to other validation studies, one paper from the QUALIFEX study also included those participants who stated never using mobile phones and set their self-reported and operator-recorded duration of to zero. In the QUALIFEX collective, Spearman's correlation coefficient was 0.63 among the mobile phone users and 0.78 when those participants who stated to be non-users were included (article 3).[112] In general, correlation coefficients were found to be substantially lower among children and adolescents (0.3 for number of calls and 0.1 for duration of calls, respectively).[162,163] These results, however,

were based on only 59 children and adolescents. In our validation study, we found correlation coefficients of 0.57 for number of calls (based on *N*=135 children and adolescents), 0.57 for duration of calls (*N*=135) and 0.41 for time since first use of mobile phones (*N*=236, Figure 8-1). With the exception of one study from Mohler et al.[112] (article 3), other studies calculated the correlations only among users of mobile phones. We also calculated correlation coefficients including those participants who stated never using mobile phones and set their self-reported and operator-recorded number and duration of calls and time since first use to zero. In those analyses, correlation coefficients were 0.93 for number of calls, 0.93 for duration of calls and 0.94 for time since first use. We think that those participants that stated never using mobile phones should not be excluded in validation studies. Naturally, those participants have no operator data and it appears logical to set their mobile phone use to zero. A certain extent of misclassification has to be expected since it is plausible to assume that some participants still used mobile phones (own or borrowed), even when they said they did not use mobile phones. The high correlation coefficients in the analyses where we included the non-users of mobile phones indicate that studies with a higher proportion of non-users of mobile phones (such as CEFALO) are expected to have less exposure misclassification than studies with a low proportion of non-users of mobile phones.

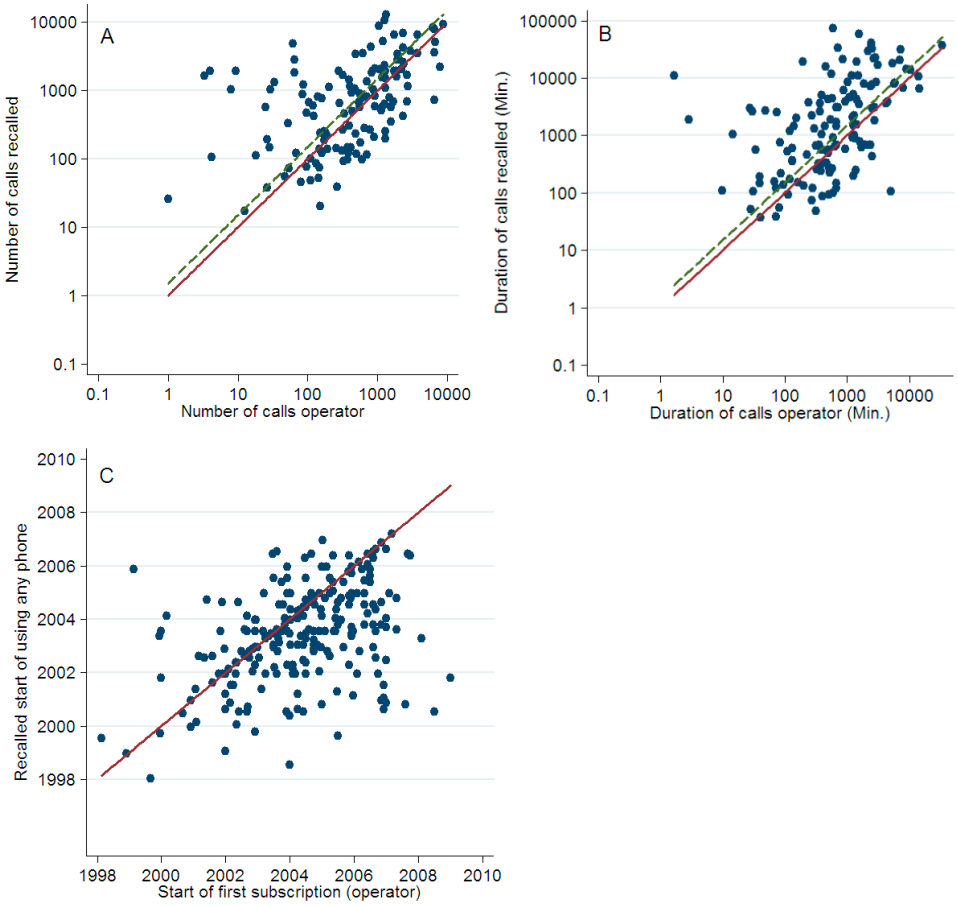

Figure 8-1 Scatterplot of (A) number of calls, (B) duration of calls (in minutes) and (C) time since first use of mobile phones self-reported against operator-recorded use. The solid line denotes the line of equality and the dashed line denotes a ratio of recalled to operator-recorded amount of use ≥1.5.

Cohen's kappa is often used to quantify the extent of agreement between self-reported and objective mobile phone use beyond the expected level of agreement by chance alone.[341] Cohen's kappa ranges from −1 (perfect disagreement) to 1 (perfect agreement) with a value of 0 denoting no agreement. In the validation studies that calculated Cohen's kappa, values ranged from 0.39[167] to 0.50[166] for number of calls and from 0.18[164]

to 0.50[167] for duration of calls. When Mohler et al.[112] included those participants who stated to be non-users of mobile phones in the analysis and set their duration of mobile phone use to zero, Cohen's kappa increased from 0.41 to 0.51. Only one study provided a kappa value of 0.30 for having a subscription or not.[168] In our validation study, Cohen's weighted kappa was 0.42 (95% CI=0.29 to 0.53) for number of calls and 0.41 (95% CI=0.29 to 0.54) for duration of calls. Many validation studies also calculated the ratio of self-reported to objectively recorded mobile phone use. A ratio of 1 denotes perfect agreement whereas a ratio >1 denotes overestimation and a ratio <1 denotes underestimation of recalled mobile phone use. The mean or median of this ratio denotes the average over- or underestimation in the study sample and the standard deviation or the interquartile range (IQR) is a measure of variation between individuals and therefore, a measure of random recall error.[166] Most studies among adults found that participants underestimated their number of calls and reported ratios of self-reported to objectively recorded mobile phone use ranging from 0.81[165] to 0.92.[166] Only one study reported that participants overestimated their number of calls by a factor of 1.7.[167] For duration of mobile phone calls, all studies found consistently that participants overestimated their phone use by a factor ranging from 1.4[165] to 2.8.[167] One study among children and adolescents reported that numbers of calls were underestimated and duration of calls was overestimated which is in line with the results of most validation studies conducted among adults.[163] Another validation study among children and adolescents found that participants overestimated their number of calls and underestimated their duration of calls.[162]

In our validation studies among 7–19 years old children and adolescents, we found that both number and duration of calls were overestimated by a median factor of 1.23 and 2.20, respectively. The corresponding arithmetic mean of the ratio was 1.63 for number of calls and 2.62 for duration of calls. Furthermore, we found that controls tended to overestimate their number and duration of calls more compared to cases. This difference was not statistically significant, however. Moreover, we found that ratios decreased with increasing operator-recorded level of mobile phone use which is

not in line with the validation among the INTERPHONE study collective.[165] The reasons for this conflicting finding are not fully understood.

A recent Australian study investigated how well adolescents remember their preferred laterality of mobile phone use.[162] The researchers used hardware modified phones (HMP) with tilt sensors to record the orientation of the handset during the calls. The agreement between the recorded and self-reported laterality was modest (Cohen's kappa=0.3, 95% CI=0.0 to 0.6). These results suggest that self-reported laterality of mobile phone use is of limited validity among adolescents. The study, however, was based on only 30 students.

One study also investigated whether or not there is a difference in quality of recall between cases and controls (i.e. differential recall errors) among INTERPHONE participants.[165] The study found no evidence for differential recall errors. The researchers found, however, that for cases but not for controls, the ratios of self-reported to objectively recorded mobile phone use increased with increasing time before the interview. Also, ratios increased with level of use among cases and controls.

In epidemiology, a common assumption is that cases are expected to overestimate their exposure more than controls, probably because they seek an explanation for their diseases and do more intensely reflect about past exposure.[342,343] In case-control studies, this would lead to an overestimation of the risk estimates. In our study, controls tended to overestimate more than cases which would lead to an underestimation of the risk estimates. The confidence intervals were wide, however, and it is doubtful whether the amount of overestimation really differed between cases and controls in the whole CEFALO collective. A limitation of our study is that operator-recorded data were only available for a subset of the CEFALO study sample. In Switzerland, network operators have to delete traffic data after six months and thus, we only got usable data for the exposure period after the reference date.

Another possibility is that brain tumor patients may have memory impairments limiting their ability to correctly recall their past mobile phone use. This could lead to an

underestimation of mobile phone use by cases compared to controls which would subsequently lead to an underestimation of the true risk estimate. This hypothesis is not supported by our validation study. We found that cases underestimated neither their number nor duration of calls. Controls were also found to overestimate both measures.

An important methodological difference between INTERPHONE and CEFALO is the way how the questions about past mobile phone use were asked. In INTERPHONE, study participants were asked to give their past mobile phone use directly in open-ended questions whereas in CEFALO, participants indicated their amount of mobile phone use on a pre-defined categorical scale (closed-ended).[22] An advantage of pre-defined categorical questions is that extreme outliers such as observed in INTERPHONE could not occur in CEFALO. On the other hand, the use of pre-defined questions limited the variation of the self-reported mobile phone use and could have led to an underestimation of heavy mobile phone use. Another possible disadvantage of pre-defined questions is that participants may have had the tendency to avoid the extreme categories, although evidence for this hypothesis is currently lacking.

Despite the many advantages, operator-recorded mobile phone traffic data also have some disadvantages. Study participants have to remember their phone numbers in order to be able to link the operator-recorded data to the participant. It is impossible to verify whether recorded calls were made or taken by the children themselves. It is possible that the child occasionally lent out his or her phone to a peer or, in contrast, borrowed a phone from someone else. Furthermore, for underage children, subscriptions were sometimes held in the name of the parents.

In summary, recall of past mobile phone use has been shown to be affected with large random errors and moderate systematic errors be it among adults, children or adolescents. Recall of number of calls was generally more accurate than recall of duration of calls. Evidence further suggests that the precision of recall decreases with increasing time before interview as well as with increasing level of use.[165] On the other hand,

little evidence for differential recall errors between cases and controls has been accumulated so far.[165] But our simulation study showed that random recall errors alone can lead to an underestimation of heavy mobile phone use even when they are non-differential. On the basis of the current evidence, the use of exclusively self-reported mobile phone use in case-control studies about mobile phone use and health outcomes is strongly discouraged. The use of self-reported mobile phone use can only be recommended in prospective studies and the use of objectively recorded mobile phone use is strongly encouraged whenever possible.

8.2 Predictors of level of mobile phone use and of precision of mobile phone recall

The possible relationship between mobile phone use among children and adolescents and various health outcomes such as behavioral problems, sleep disturbances, and perceived stress has been addressed by only few studies.[91,99,344-351] The use of self-reported mobile phone use was still the most prominent method of exposure assessment in these studies. Some of the studies also used objective exposure data. Because of the known inaccuracy of self-reported mobile phone use, results of studies relying solely on self-reported exposure data must be interpreted with caution.

Up to date it is not clear whether some health-related factors are associated with poor estimation of own mobile phone use. Factors that are both related to health as well as poor estimation of mobile phone use could act as confounders in studies relying solely on self-reported mobile phone use. Examples of such health-related factors are sex, age, and socioeconomic status (SES).

Only one study addressed the possible predictors of level of mobile phone use among adolescents.[352] The study did not, however, investigate possible factors related to recall precision of own mobile phone use. The researchers found that a higher parental socioeconomic status was associated with a higher probability for current use of mobile phones. Adolescents of parents that expressed serious concerns about possible health

effects of mobile phone use were more likely to regularly use them. The level of mobile phone use was statistically significantly related to personality traits of the adolescents. High scores of psychoticism were related to higher probability of regular use of mobile phones (OR=1.06, 95% CI=1.01 to 1.11).

In our study, level of mobile phone use was related to country. Swedish children and adolescents had a statistically significantly lower number of calls per day than participants from Denmark. Other factors were not statistically significantly related to level of mobile phone use. Average mobile phone use increased with increasing age (7% per year of age) and decreased with increasing parental SES. These relationships failed to reach statistical significance. Naturally, we expected mobile phone use to increase with age. The result is probably explained by the fact that we used average mobile phone use for each participant during all subscription periods. Therefore, increasing use with age is expected to be diluted with rare use during early subscriptions. Since our study sample was rather small (48 case patients and 87 control subjects), the statistical power to detect small effects was limited. Inyang et al.[352] reported a tendency of higher levels of mobile phone use among adolescents of parents with a higher SES. The relationship was, however, also not statistically significant.

No studies so far used objectively recorded data to assess possible predictors of precision of own mobile phone recall among children and adolescents. We found that participants aged 15–19 years had a higher likelihood of overestimating their cumulative number and duration of calls compared to participants aged 7–14. In addition, being female was associated with higher probability to overestimate the duration of calls (OR=2.76, 95% CI=1.22 to 6.24). Importantly, the likelihood of overestimating did not statistically significantly differ between cases and controls.

In conclusion, we found evidence that health-related factors such as age and health are related to the amount of errors in reported mobile phone use in children and adolescents. Such factors could act as confounders and should be considered in the statistical analysis. On the other hand, we found little evidence for a difference in mobile

phone recall precision between cases and controls (i.e. differential recall bias). In the light of the substantial reporting error of self-reported mobile phone use and because of possible confounders, we emphasize the use of objectively recorded mobile phone use from network operators of from software modified phones (SMP) or alike.

8.3 Mobile phone use and brain tumor risk

All studies investigating mobile phone use and brain tumor risk so far were conducted among adults. CEFALO is the first case-control study about the use of mobile telephones and brain tumor risk among children and adolescents and therefore, fills an important gap.[353] In summary, our study does not suggest that there is a causal relationship between mobile phone use and brain tumor risk among children and adolescents of age 7 to 19 years. We found no consistent exposure-response relationship either in terms of the amount of mobile phone use or by the location of the tumor. This finding is in line with the results of the majority of studies about mobile phone use and brain tumors among adults.[21,26,354] We found, however, a significant dose-response relationship for time since first subscription when we used the data recorded by the network operators (OR=2.15, 95% CI=1.07 to 4.29 for >2.8 years since first subscription, p_{trend}=0.001). This estimate was based only on 163 participants because operator-recorded time since first subscription was only available for 35% of case patients and 34% of control subjects who reported to own a subscription. In addition, there was no consistent trend with cumulative duration or number of calls in the analysis with operator data and the sample size was even lower in those analyses. Reverse causality may also be considered when interpreting the increased risk for time since first subscription. Reverse causality exists when it is difficult to determine the exact date of the onset of the condition, such as brain tumors.[355] Because of prodromal symptoms before diagnosis, some case patients may have appeared frailer than healthy children.[356,357] To provide frail children better protection, parents may have given them a mobile phone to use in case of emergency, leading to earlier subscriptions for case patients compared to healthy children. Last but not least, we com-

puted over 100 odds ratios using an alpha of 0.05. Hence, one would expect some spurious statistically significant odds ratios due to chance (i.e. type 1 error).

Because it is unclear which exposure surrogate (e.g. cumulative number of calls, cumulative duration of calls, time since first use) might be relevant for health, analyses are usually performed using several exposure metrics. Of course, these exposure metrics are highly correlated among each other because they all reflect past mobile phone use. Indeed, Spearman's rank correlations between the various exposure metrics ranged from 0.8 (regular use vs. time since first use) to 0.98 (total number of calls vs. total duration of calls). Therefore, all odds ratios are expected to be fluctuating around the odds ratio for regular use (OR=1.36). In the case of a causal association between mobile phone use and brain tumor risk, however, one would expect to observe an exposure-response relationship. We failed to detect such a pattern in CEFALO. Therefore, it is likely that the observed statistically non-significant increase in brain tumor risk among regular users most likely represents random variability.

The odds ratio for regular use was considerably lower for Norwegian children and adolescents compared to participants from the other countries (OR=0.51 for Norway vs. 1.49, 1.73 and 1.69 for Denmark, Sweden, and Switzerland). The pattern was in line with random variability, however (*p*-value for heterogeneity=0.20). The reasons for the lower odds ratio for Norway are not fully understood but is has to be assumed that selection bias and other methodological shortcomings were at play. Out of all participating countries, Norway had the lowest participation rates among cases and controls (65.7% and 58.2%, respectively). Moreover, Norway contributed only 44 out of 352 (12.5%) cases and 78 out of 646 (12.1%) controls.

8.3.1 Considerations regarding biological mechanisms of carcinogenicity

There is still no known mechanism of how mobile phone radiation may cause brain tumors or other cancers.[19,63,81,353] The only known effect of mobile phone radiation is the heating of the tissue.[3] Many *in vivo* and *in vitro* studies, including studies in mouse

and rat models do currently not corroborate the assumption that exposure to RF-EMFs is carcinogenic.[78-80] Moreover, the applicability of results from experimental studies on cell cultures or animals to humans is questionable. The distribution of RF energy within the brain is well-known from dosimetry and modeling studies.[16,202,203,358-365] The absorbed energy is highly localized and virtually confined to the brain hemisphere on the side were the mobile phone is held (Figure 1-10). Because of the absence of an established biological mechanism, the most plausible assumption is that brain tumors are more likely to occur in the brain hemisphere on the side were the mobile phone handset is mainly held (i.e. ipsilateral mobile phone use).[366,367] A relationship between the use of mobile phones and tumors occurring near the location of the handset would denote stronger evidence for a causal relationship than an association with more distant tumors.[21] The INTERPHONE study reported mostly greater odds ratios for ipsilateral than for contralateral use of mobile phones. There was, however, no clear exposure-response relationship. The higher risk estimates for ipsilateral use may be due to cases that overreported use on the side of the tumor. In our study, we found higher risk estimates for contralateral use of mobile phones compared to ipsilateral use. In addition, we found protective risk estimates in the subset of participants with a central brain tumor or a tumor with unknown location. The reasons for these counterintuitive findings are not fully understood. Studies provide evidence, however, that case patients appear to overreport mobile phone use on the side of the tumor.[21,367] In general, self-reported laterality of mobile phone use seems to be affected by recall errors and is of limited validity, especially in children and adolescents.[162]

We found no exposure-response relationship in terms of the location of the brain tumor. The brain regions that are known to absorb most of the RF energy from mobile phones are the temporal and frontal lobes and the cerebellum (Figure 1-11).[202] While the self-reported laterality of mobile phone use is not very reliable, analyses of tumor location are thought to be less susceptible to recall bias.[21] We found an odds ratio of 1.00 (95% CI=0.58 to 1.72) when we investigated only those case patients with a tumor in the temporal and frontal lobes and in the cerebellum. A statistically significantly increased odds ratio of 1.92 (95% CI=1.07 to 3.44) was observed for tumors that oc-

curred in other regions than the temporal or frontal lobes or the cerebellum. As for the laterality of the use, one would expect the highest risk estimates in those brain regions where most of the RF energy is absorbed. INTERPHONE found higher odds ratios for tumors in the temporal lobe compared to other lobes but the confidence intervals of the lobe-specific estimate were wide.[21]

The fact that most childhood brain tumors are diagnosed in the first five years of age argues against a causal relationship between mobile phone use and brain tumors. The amount of mobile phone use in the first five years of life is virtually absent or very low and induction periods as short as 1–5 years are highly unlikely. For brain tumors occurring during childhood or adolescence, latency periods can obviously not be as large as 20 to 40 years. Only 1% of all childhood brain tumors are present at birth or are diagnosed within the first few months of life but the majority of brain tumors occur before the age of five years.[177-179] This suggests that both pre- and postnatal exposures should be considered. Several carcinogenic and non-carcinogenic chemical compounds have been found to be able to cross the placental barrier and interact with DNA in the developing fetus.[178,179] Regarding RF-EMFS, studies that modeled fetal absorption of radiofrequency fields concluded that the exposures are likely to be low and not high enough to elevate the body temperature of the fetus.[365,368,369] A recent study in rat models found no evidence for a teratogenic effects of *in utero* WI-FI exposure, even at the highest level of 4 W/kg.[370] These results further corroborate the evidence that exposure to mobile phone-related RF-EMFS at levels below standard limits are not teratogenic.[78,80,371] Moreover, there is currently no known biological mechanism that could explain the relation between exposure to mobile phone radiation *in utero* and the occurrence of childhood brain tumors. No studies have investigated prenatal mobile phone exposure and childhood brain tumors so far. The collection of objective exposure data of the fetus *in utero* is another unsolved challenge.

The retrospective case-control design has been criticized because of the many potential methodological caveats such as recall and selection bias.[24,372,373] Indeed, recall of past mobile phone has been shown to be affected with large random errors, even if the

recall period is as short as six months.[166] The participation rates in CEFALO were very high (83% for case patients and 71% for control subjects) compared to other case-control studies such as INTERPHONE (70% for case patients and 53% for control subjects).[21] Thus, relevant selection bias was unlikely to play a big role in CEFALO. Furthermore, we assessed the impact of numerous potential confounders on the analyses within CEFALO. None of the considered confounders had a meaningful impact on the risk estimates. It is therefore rather unlikely that confounding played a major role in CEFALO although it is possible that we missed some important but still unknown confounders. There is consensus among epidemiologists that further retrospective studies such as case-control studies will not contribute to clarification of the question of whether mobile phone use is causally related to brain tumor development. Future studies with objective exposure assessment or the use of prospectively collected exposure data are warranted. The Holy Grail, so to speak, of exposure assessment would be to have precise data about the amount of absorbed RF energy in the brain. Exposure surrogates such as cumulative number and duration of calls are only crude surrogates for the amount of absorbed RF energy. Output power from mobile phones that use the UMTS network, for example, is 100 to 500 times lower on average than that from GSM phones.[7,8] In the most extreme situation, a study participant who used a UMTS phone to make 500 cumulative numbers of calls could have the same actual RF exposure as a participant who used a GSM phone to make one call. One study, in search of the Holy Grail, attempted to estimate the RF energy absorbed in the brain from mobile phones in the INTERPHONE study concluded that amount and duration of mobile phone use are important determinants of RF energy absorption but their impact can be dramatically modified by network system, frequency band and location in the brain.[358] And so the Holy Grail remains unfound up to date, it appears.

Despite the heavy criticism of the methodology of case-control studies about mobile phone use and brain tumor risk, the results of case-control studies are mostly in line with the results from a large Danish subscriber cohort study including all Danes aged 18 or more that were born in Denmark after 1925. The study found no evidence for an increased risk for brain tumors among the long-term users (≥13 years) of mobile

phones.[60-62] Furthermore, no indication of an exposure-response relationship either by years since first subscription or by anatomical location of the tumor was observed.

8.3.2 Brain tumor incidence rate trends

Probably the most convincing evidence against a causal relationship between mobile phone use and brain tumors comes from studies that assessed time trends in brain tumor incidence rates. Various nationwide studies investigated brain tumor incidence rate trends.[23,43-53] These studies covered large time periods and thus contain brain tumor patients that are long-term users of mobile phones (i.e. 10–15 years). Consistently, these studies found no evidence for a causal relationship between mobile phone use and brain tumor risk for either gender or any specific age group. In a study in the United States, Inskip and colleagues[46] found that brain tumor incidence rates were downward or flat between 1992 and 2006 (the period where mobile phones became popular and wide-spread, Figure 1-1). The researcher found, however, a significant increasing trend among 20 to 29 years old women between 1992 and 2006. This increase was driven by a rising incidence of frontal lobe tumors. Importantly, no increase of tumors in the temporal lobe, the brain region where most of the RF energy of mobile phones is absorbed, was observed. One study from Australia reported statistically significantly increasing incidence rates between 2000 and 2008 of glioblastoma multiforme and meningioma, particularly after 2006.[54] The incidence rate of glioblastoma multiforme was statistically significantly increasing overall and in the subgroup of persons aged ≥65 years. Among women aged ≥65 years, no statistically significant increase of glioblastoma incidence was seen. Overall, meningioma incidence rates were statistically significantly increasing in men but not in women. Among persons aged 20–64 years, no overall increase in meningioma incidence rates could be observed. There was, however, an increase in meningiomas among men but not among women. The incidence rates of acoustic neuroma (i.e. vestibular schwannoma) were found to be statistically significantly decreasing overall and among women.

A potential increase in brain tumor incidence is a function of the magnitude of the shift of the age-incidence function and its slope.[373] If the tumor growth constant is increased by a factor *f*, the shift of the age-incidence function is $s=(f-1)\times t_m$ with t_m being the duration of mobile phone use (for a detailed derviation and proof see Kundi 2011[373]). Hence, an increase of tumor growth by 50% (f=1.5) will result in a shift of the age-incidence function of 50% of the duration of mobile phone use. Furthermore, the odds ratio for brain tumor cases observing a shift in the incidence function by a fraction of the duration of mobile phone use is $e^{(\gamma \times s)}$ with γ being the slope of the age log-incidence function and s the shift in years by the increased tumor growth rate.[373] Moreover, the overall incidence at age A is given by $e^{(\beta+\gamma A)} \times \left[1-\pi+\sum_s \pi_s \times e^{(\gamma \times s)}\right]$ with π_s being the fraction of mobile phone users with a shift of s.[373] Given the observed increase in glioblastoma incidence by Dobes et al.[54] from 3.22 to 3.96/100'000 PY between 2000 and 2008, one can use the aforementioned formulas to calculate the factor f by which mobile phone use must increase tumor growth to explain the observed increase in the incidence rates. For the following calculations, I used a slope of the age log-incidence function of 0.05 $\log_e$ units per year (the age log-incidence function is fairly linear within the range of 30 to 60 years of age).[373] Furthermore, I used the distribution of duration of mobile phone use of the glioma controls in the INTERPHONE study. Among the glioma control subjects, 36.3% (1078/2972) were never regular users of mobile phones, 8.3% (247) had a use of 1.45 years on average, 24.4% (725) had a use of 3 years, 23.2% (690) had a use of 7.5 years and 7.8% (232) had a use of ≥10 years (I assumed a use of 10 years for this group).[21] Under these assumptions I got a factor of f=2.11 which means that mobile phone use must increase tumor growth by 111% (i.e. double tumor growth) to causally explain the observed increase in glioblastoma incidence of 3.22 to 3.96/100'000 PY (Δ=0.74/100'000 PY). The corresponding hypothetical odds ratios are: 1.08 for a use of 1.45 years of mobile phone use, 1.18 for a use of 3 years, 1.52 for a use of 7.5 years and an odds ratio of 1.75 for a use of 10 years. On the basis of current studies and in the light of a still missing biological mechanism of carcinogenicity, I consider a doubling of tumor growth caused by mobile phone use highly implausible. Although the distribution of duration

of mobile phone use in the example above was rather conservative, a recalculation assuming 10% never regular users of mobile phones, 25% with a use of 1.45 years, 25% with a use of 3 years, 20% with a use of 7.5 years and 20% with a use of 10 years still resulted in a large increase factor of f=1.85 denoting an increase in tumor growth due to mobile phone use by 85%. The corresponding odds ratios are: 1.06 for a use of 1.45 years, 1.14 for a use of 3 years, 1.38 for a use of 7 years and 1.53 for a use of 10 years. On the basis of these calculations, I argue that the increase in glioblastoma incidence rates observed by Dobes et al.[54] is unlikely to be causally related to the use of mobile phones.

Several studies used joinpoint regression models (piecewise log-linear models) to analyze time trends in brain tumor incidence rates. In joinpoint regression, the model searches for points in time (i.e. joinpoints) where changes in incidence rate trends occur.[374] Usually, no constraints on the position of the joinpoints are made. Two recent studies that analyzed brain tumor incidence rates from Denmark, Finland, Norway and Sweden between 1974 and 2008 using joinpoint regression models found no evidence for an increase of incidence rates between 1998 and 2003, the time when possible associations between mobile phone use and brain tumors would be informative (induction period of 5 to 10 years).[23,45] Another study from England also found no evidence for an increase in brain tumor incidence rates between 1998 and 2007.[50] An important conclusion that can be drawn from studies that addressed time trends in brain tumor incidence is that risk estimates for astrocytoma of 4.4 (95% CI=1.9 to 10) and 5.2 (95% CI=2.2 to 12) for cordless and mobile phone use before the age of 20, respectively, are clearly incompatible with the observed incidence rate trends.[23,30,43]

In CEFALO, we used the observed brain tumor incidence data of Swedish children and adolescents aged 5–19 years from 1990 to 2008 and added hypothetical incidence rate trends derived from the observed risk estimates for regular mobile phone use based on self-reported data (OR=1.36, 95% CI=0.92 to 2.02). In addition, we also included hypothetical incidence rates based on the observed significant odds ratio of 2.15 (95% CI=1.07 to 4.29) for more than 2.8 years since first operator-recorded subscrip-

tion.[375] We found that a risk estimate of 2.15 after 3 years of regular mobile phone use is expected to increase the incidence rate by about 50% in the last 10 years based on the proportion of regular users in the CEFALO collective. No such trend, however, was observed in the incidence rates (Figure 8-2). This finding does not indicate that short-term use of mobile phones causes brain tumors among children and adolescents. Thus, the results from CEFALO are in line with those of other studies that investigated brain tumor incidence rate trends.

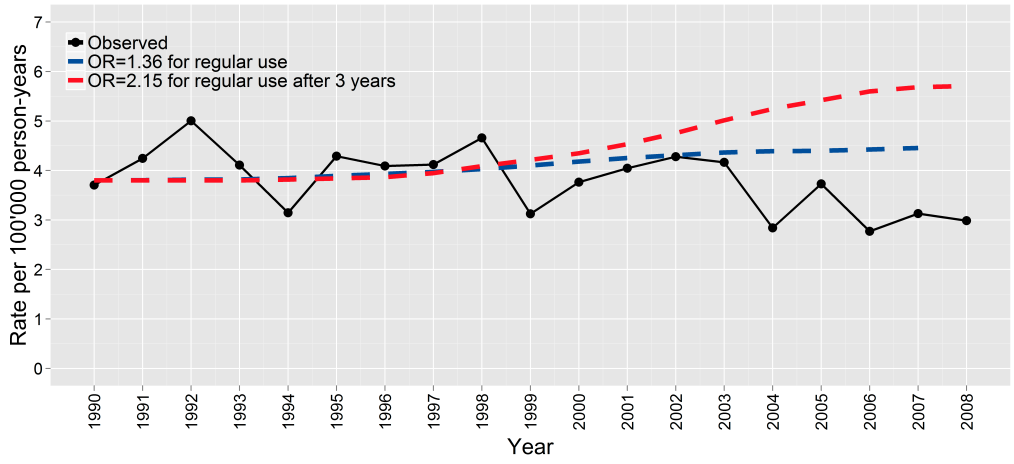

Figure 8-2 Gender and age-standardized incidence rates among Swedish children and adolescents aged 5–19 years between 1990 and 2008 (solid line). The dotted lines denotes hypothetical incidence rate trends under the assumption that regular use of mobile phones increases the risk of brain tumors by 36% (without a latency period) and by 115% after 3 years of regular mobile phone use.

In a recent commentary, Söderqvist et al.[376] disagreed with our conclusion that the results of CEFALO do not point to a causal relationship between the use of mobile phones and brain tumor risk among children and adolescents. In contrast to our interpretation, the authors see "[...] several indications of [an] increased risk, despite low exposure, [and a] short latency period [...]".[376] They further claimed that the risk estimates in CEFALO are underestimated because of exposure misclassification due to

cordless phone use and because of the fact that use of wireless phones among adolescents is nowadays larger compared to the amount of use during the study period of CEFALO (2004–2008). Söderqvist and colleagues fail, however, to provide an explanation of how such increased brain tumor risks correspond to the stable incidence rate trends in the Nordic countries over the last 20 years (Figure 8-2 and Figure 8-3). The discrepancy becomes even more striking under the assumptions of short latency periods combined with large risks for low exposures.[23] The same reasoning can be applied concerning the results of the most plausible scenarios of our simulation study. The most plausible scenarios implied the possibility of underestimating the risk estimates for heavy mobile phone use in CEFALO. These results lie in contrast with the stable brain tumor incidence rate trends observed in many countries.

Some authors repeatedly implied that conclusions about brain tumor incidence trends of children and adolescents are not meaningful on the basis of data from the Swedish Cancer Register because of an alleged underreporting of nervous system tumors.[376,377] A study investigating the completeness of the Swedish Cancer Register, however, concluded that the overall completeness of the Swedish Cancer Register is high and an underreporting of nervous system tumors was mainly confined to patients of age 70 years or older.[378] Hence, it can be reasonably assumed that the observed brain tumor incidence rate trends among Swedish children and adolescents reflect reality. Furthermore, no increase in brain tumor incidence rates of children and adolescents aged 5 to 19 years living in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden) can be observed for the period of 1990 to 2009 (Figure 8-3). Based on the fact that the Swedish Cancer Register was found to be exhaustive in terms of brain tumor cases in the age group of children and adolescents, it is unlikely that an underreporting of brain tumor cases among children and adolescent is large enough to hide an underlying increasing trend.[378]

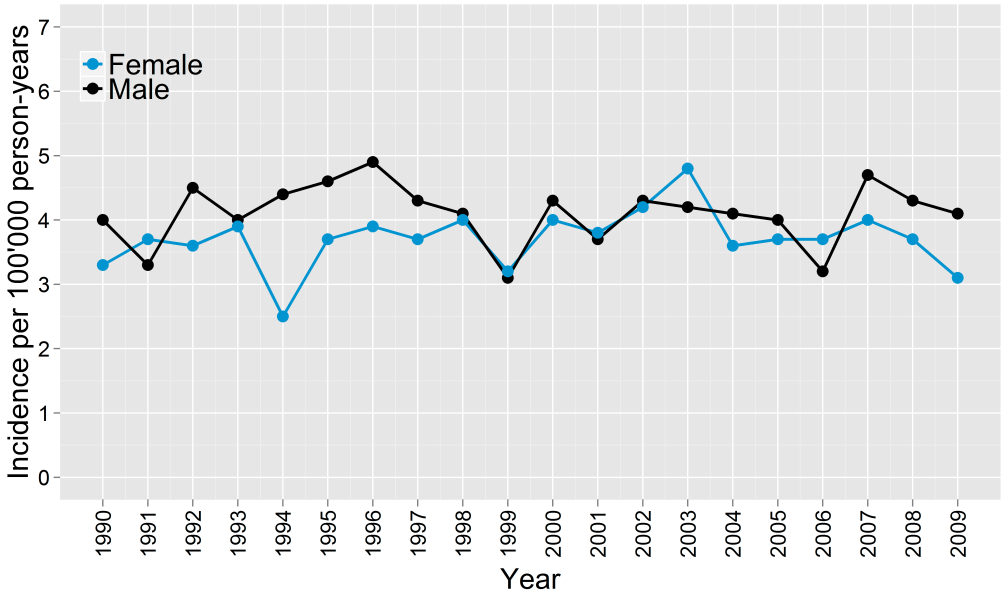

Figure 8-3 Age-standardized incidence rates for brain and central nervous system tumors for the age group 5–19 years living in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) obtained from NORDCAN (www-dep.iarc.fr/nordcan/English/frame.asp, accessed January 9, 2012).

8.3.3 Remaining uncertainties

The evidence from time series studies is reassuring but there is still the possibility that mobile phones are causally related to brain tumor occurrence. The uncertainty, however, concerns mainly the long-term and heavy use of mobile phones which is reflected in the fact that the International Agency for Research on Cancer (IARC) recently classified RF-EMFS as "possibly carcinogenic to humans" (Group 2B).[142] This means that there is limited evidence from human studies and less than sufficient evidence from experimental animal studies. The IARC classification of RF-EMFS in the group 2B may seem dramatic but one has to bear in mind that coffee, for example, is classified in the same group (for urinary bladder cancer). Concerning mobile phones it is evident from current studies, including CEFALO, that the risk for brain tumors cannot be

large, especially for short-term use (<10 years). Recent studies about mobile phone use and brain tumor risk such as the INTERPHONE study cover a large number of brain tumor patients that were short-term users. Hence, these studies had enough statistical power to detect high risks for short-term mobile phone users.

Because of the high heterogeneity of brain tumors, it may be possible that the use of mobile phones increases the risk only for certain types of brain tumors.[211] In both cases – a small increase of brain tumor risk in general and an increase in risk only for a special brain tumor type – the number of excess brain tumor cases would probably not be large enough to be detected over background variation in incidence rates. In addition, it may be argued that the latent period of brain tumors caused by mobile phone usage is longer than 10 to 15 years.[373,379] Average latent periods have been estimated to be 20 to 30 years for glioma and 20 to 40 years for meningioma, respectively.[380-382] For acoustic neuroma, latent periods are estimated to be around 25 years.[383] The latency times, however, follow a certain distribution and some brain tumor cases are expected to become incident much earlier than the average latency time due to chance and inter-individual variability in genetics and environmental factors. As the penetration rate (percentage of mobile phone subscriptions divided by the population) approaches or even exceedes 100% in many countries worldwide, one would nonetheless expect an increase in the incidence rates, especially for a high risk of short-term mobile phone use. A recent simulation study using data from INTERPHONE calculated the probabilities of detecting an increase in brain tumor incidence rates among men aged 40–59 years in Denmark, Finland, Norway, and Sweden assuming different relative risks (0.8, 1.1, 1.2, 1.5 and 2.0) for mobile phone users and different induction periods (1, 5, 10, and 15 years).[23] The results conveyed that relative risks of 2.0 for an induction period up to 15 years, 1.5 for up to 10 years, and 1.2 for up to 5 years had a probability of 100% of being detected and are therefore incompatible with the observed incidence rate trends.[23] For small relative risks combined with longer induction periods such as RR=1.2 with an induction period of 15 years or RR=1.1 with an induction period of 5 years or longer, the probabilities of detection were smaller and still compatible with the observed incidence rates. For heavy users that accumu-

lated more than 1640 lifetime hours of mobile phone use, relative risks of 2.0 for an induction period up to 5 years, and a relative risk of 1.5 for up to 1 year were also found to be incompatible with the observed brain tumor incidence rates.

Another simulation study compared observed incidence rates of glioma in the United States with projected rates for 1997–2008.[43] The researchers found the incidence rates to be constant between 1992 and 2008, the period where mobile phones use increased from 0% to nearly 100% in the US population (Figure 1-1). The study further concluded that higher glioma incidence rates would be expected than the observed ones if mobile phone use was related to glioma risk, even with a long latency period of 10 years and a low relative risk of RR=1.5. Importantly, the authors could clearly rule out the results from a Swedish study by Hardell and colleagues[36] as the predicted incidence rates should have been at least 40% higher than the observed rates in 2008.[43] The authors could not, however, rule out the increased glioma risks that were found in INTERPHONE for a small proportion of highly exposed people.[21]

In addition to mobile phones, other possible exposures were studied within the CEFALO collective. No systematic pattern was observed regarding exposure to animals whereas maternal farm-residence during pregnancy was found to be protective for brain tumors (OR=0.40, 95% CI=0.19 to 0.88; article 5). In another study that used data from CEFALO, little evidence was found that social contacts in early life influence the likelihood of childhood brain tumors among children and adolescents (article 6). The same study found some evidence that children with ≥4 sick days with infectious diseases per month in the first six years of life were at higher risk for brain tumors compared to children with one sick day or less per month (OR=1.91, 95% CI=1.22 to 3.01). This observed relationship, however, is thought to reflect recall bias or inverse causality.

Finally, one may ask the obvious question why the search for an association between mobile phone use and brain tumors exists in the first place. Numerous other plausible factors were studied, often with negative or inconclusive results (Table 1, page 53). The

origin of the research about mobile phones and cancers was rather the concern that there may be an interaction between RF-EMFs and human physiology that has been missed than a biophysical hypothesis or an observed increase in brain tumor incidence rates.[354] The extensive negative results concerning other possible risk factors for brain tumors make it even less likely that the use of mobile phones is causally related to brain tumor risk among children and adolescents or adults. Many of the studied factors are actually much more plausible in terms of biological mechanisms than mobile phones (e.g. transplacental molecules).

In conclusion, there is little evidence for a causal relationship between short-term (<10 years) and regular mobile phone use and brain tumor risk among children, adolescents and adults. Uncertainties remain regarding low relative risks combined with long induction periods as well as long-term (≥10 years) and heavy mobile phone use as some studies reported elevated risk estimates.[26-28,37] In addition, middle-aged adults that begun to use mobile phones in their childhood or adolescence do currently not exist because wide-spread use of mobile phones started roughly in the mid-1990s (Figure 1-1). Furthermore, although CEFALO was statistically underpowered to detect small risk increases among the short-term users, it can be concluded that a risk increase for short-term mobile phone use among children and adolescents is small, if it exists at all. The monitoring of trends in brain tumor incidence rates from population-based cancer registry data seems the most promising way to address the question whether or not the use of mobile phones increases the risk for brain tumors in any age group. Because mobile phones ownership and use has become very common among adults but also among today's children and adolescents in most countries worldwide, even a small increase in brain tumor risk should be reflected in future incidence rate trends.

8.3.4 Strengths and limitations of CEFALO

CEFALO is the first study that examined the relationship between mobile phone use and brain tumor risk among children and adolescents. In addition to the self-reported mobile phone use, we also included objectively recorded mobile phone data from network operators. Operator recorded data are considered more reliable and less prone to recall bias than self-reported exposure data. Furthermore, we also included brain tumor incidence rate trends to check whether our risk estimates are consistent with the observed trends in incidence rates of Swedish children and adolescents in this age group or not. A study has shown that the completeness of the Swedish cancer register is high and no relevant underreporting of childhood brain tumors is present.[378] The childhood incidence rates from Sweden are also consistent with the incidence rates of other Nordic countries (Figure 8-3). Hence, the Swedish incidence rates are a valuable instrument to check the consistency of the results obtained in CEFALO.

The limitations of CEFALO include the use of self-reported mobile phone use and the low statistical power to detect small increases in brain tumor risk. Moreover, operator recorded mobile phone data was only available for a subset of CEFALO participants. Also, operator recorded data have limitations themselves. They fail to account for the fact that children may have borrowed phones from peers or lent out their phones. In addition, whether or not hands-free devices were used during a call remains unknown too. Moreover, subscriptions were sometimes held in the name of the parents for underage participants. Furthermore, the amount and duration of mobile phone use among the CEFALO collective was relatively small and may has increased in this age-group since the study period (2004–2008). For example, 8% of participants aged 12–15 years at the time of diagnosis were already regular users at the age of 10, whereas this was true for only 2% of participants aged 16–19 years at the time of diagnosis. In addition, most participants in CEFALO used GSM type mobile phones, whereas the use of UMTS phones is becoming more popular and widespread nowadays. Because the average power output of UMTS phones is 100–500 times lower than that of typical GSM

phones, the actual time-weighted exposure of the brain to RF-EMFs may even have decreased in more recent years despite the increased use of mobile phones.

8.4 Public health relevance

The ownership and use of mobile phones have become ubiquitous in most countries around the world, including developing countries, and continue to grow steadily.[384] Mobile phone use among children aged 9–10 years or even use before school age is not uncommon these days.[10-13] Moreover, the sales of smartphones and other wireless devices such as tablet PCs continue to increase. As children and adolescents begin to use mobile phones and other wireless devices earlier in their lives, the cumulative lifetime exposure of children and adolescents can be expected to increase. In addition, mobile phones are often the only available possibility for communication in developing countries.[385,386] Mobile phones also became of interest for medical treatment, drug adherence and compliance and for smoking cessation programs.[387-398] Daily and weekly SMS messages sent to children and adolescents with type 1 diabetes mellitus increased diabetes self-efficacy and adherence to treatment and achieved a high level of satisfaction among the users.[399] Because of the high exposure prevalence, even a small increase in brain tumor risk related to mobile phone use could lead to meaningful numbers of excess case patients, even though brain tumors are still a rare disease. Recent advances in neurosurgical and neurodiagnostic techniques and radiation therapy have led to an increase of the 5-year relative survival rate of childhood brain tumors from 58% to nearly 63% in the period from 1975 through 1995.[47,181,212] However, childhood brain tumors are more often malignant compared to adult brain tumors (65.2% vs. 33.7%) and survivors of childhood brain tumors often face neuropsychological, cognitive, and endocrine impairments.[181,188,400-405] In a survey on tumors in the first year of life, severe neurological deficits were found among 10.8% of survivors.[197] In the same survey, 14.4% of survivors were found to suffer from seizures and had a higher likelihood of unemployment (OR=10.8). Furthermore, survivors of childhood brain tumors had a higher likelihood to be unable to drive (OR=28.8) and to de-

scribe their current health as poor (OR=7.8).[197] Another study found that 66% of survivors with supratentorial and 90% of children with infratentorial brain tumors were able to lead a normal life.[406] Thus, even a modest increase in childhood brain tumor incidence would have a meaningful impact on public health. The anticipated increase of exposure to RF-EMFs of mobile phones could, however, be attenuated by the increasing spread of UMTS phones. The widespread use of UMTS phones could indeed lead to a substantial decrease of actual exposure to RF-EMFs from mobile phones as the average output power is up to 100–500 times lower than that of GSM phones.[7,8]

Fears of adverse health effects of mobile phones continue to persist in the general public despite the substantial body of scientific literature that has been published so far.[92,106,107,407] The uncertainty regarding long-term and heavy use of mobile phones and the lack of an established biological mechanism of carcinogenicity as well as conflicting study results continue to fuel public concern. On the other hand, wireless devices such as mobile phones experience a dramatic increase in popularity and ownership and have numerous advantages that make our daily lives more convenient. In addition, mobile phones have the potential to play an important role in public health, especially in developing countries.[393-398] With respect to the current evidence about adverse health effects of mobile phones, it can be reasonably assumed that the benefits outweigh possible risks.[408] Recently, some studies provided convincing evidence that electromagnetic fields inhibit cancer cell proliferation and are effective in treating liver cancer.[83-85] Importantly, some studies have found that electric fields stop cell proliferation in human brain tumors and metastatic spread of lung tumors.[86,87] However, the frequencies of the fields used in these studies are different from the frequencies of mobile phones.

It is known that worries about adverse health effects of mobile phone radiation themselves can lead to certain health impairments. This phenomenon is known as *nocebo effect* which can be interpreted as the inverse of the well-known placebo effect.[92,104,130,131,134] This suggests that health impairments attributed to radiofrequency fields are caused by psychological rather than biophysical mechanisms. Brain tumors

are obviously not among such health impairments. Whether health impairments attributed to RF-EMFs are due to biophysical mechanisms or are in fact nocebo effects, electromagnetic hypersensibility is of public health relevance as more and more individuals attribute their health symptoms to exposure to electromagnetic radiation.[103]

An increasing number of studies are published nowadays that concentrate on psychological rather than biophysical effects of information technology use in general and mobile phone use in particular. Studies addressed the relationship between prenatal exposure to mobile phones and behavioral problems in children. These studies reported increased risks for behavioral problems associated with pre- and postnatal exposure to mobile phones.[91,344,409] These results, however, should be interpreted with caution as no biological mechanisms are known that could explain these associations. Furthermore, confounding and recall bias prevent a causal interpretation. Another study found no evidence for a relationship between prenatal exposure to mobile phones and motor or cognitive/language developmental delays among children at 6 and 18 months of age.[345] Nonetheless, mental health problems among young people have been increasing around the world.[410] Emerging issues of mobile phone use include perceived stress due to information overload and constant availability, behavioral problems in children, concentration problems in children, and increased risk of motor vehicle accidents.[411-416] Recent prospective cohort studies have indeed found an association between frequent use of mobile phones and mental health problem among children and adolescents.[97,98]

9 Outlook

There are still uncertainties regarding long-term and heavy use of mobile phones and brain tumor risk among children, adolescents and adults. CEFALO, being the first study about mobile phone use and brain tumor risk among children and adolescents, fills an important gap in research.[353] Because of the methodological challenges of retrospective case-control studies about health effects of mobile phone use, large prospective cohort studies that use prospectively collected exposure data to avoid recall bias and allow for sufficient latency periods to prevent reverse causality are warranted.[355] COSMOS (cohort study of mobile phone use and health) is such a prospective cohort study that aims to follow 250'000 European mobile phone users of ≥18 years of age over a period of over 25 years.[417] The main COSMOS study was launched in the UK in April 2010. COSMOS aims to unveil possible long-term effects of mobile phone use and will have multiple health outcomes such as cancer risk, sleep disorders, headaches, and neurological and cerebro-vascular diseases. Another large cohort study is the Danish cohort study of which the newest update has recently been published.[60]

The accurate assessment of mobile phone exposure will be the Achilles' heel in all future studies about mobile phone use and health outcomes. Energy output and therefore amount of absorbed RF energy differs substantially between network systems such as GSM and UMTS.[358] Because different communication systems are used concurrently, it is difficult to estimate the true amount of energy absorbed by the brain for any individual and it is unclear which exposure measure is the best proxy (e.g. cumulative number of calls, cumulative duration of calls, time since first use, cumulative subscription time etc.). Technical development in wireless communication

advances rapidly and a change in network technology could change the exposure situation of individuals. The fourth network generation, LTE (long term evolution), is currently being introduced in many countries.[9] Up to date, LTE contributes only a minority to the cumulative exposure from RF-EMFs.[418,419] Exposure levels of LTE seem to be of similar magnitude as those from GSM and UMTS networks but it is not clear yet how the exposure situation will change with the widespread introduction of LTE. New technologies such as beamforming will complicate exposure assessment excessively introducing even more uncertainty. Beamforming is a technique that allows changing the direction of the reception or transmission of a signal.[420] In addition, consumer behavior is also subject to rapid change. The functionality of modern smartphones and other wireless devices goes far beyond mere calling and texting. Modern wireless devices provide constant access to the internet and the extension of functionality is likely to lead to an increase in ownership and amount of use of such devices across wide age groups.

Large cohort studies that are sufficiently powered to provide robust statistical results and featuring prospectively collected exposure data are warranted to clarify the possible link between mobile phone use and health outcomes. It is crucial that future studies put an emphasis on accurate exposure assessment. This means that important determinants such as the network system have to be taken into account.[358] Moreover, monitoring of trends in brain tumor incidence rates from population-based cancer registry data is the most promising way to investigate whether the use of mobile phones increases brain tumor risk or not. Finally, further studies about short and long-term psychological rather than biophysical effects are warranted. Mental and behavioral problems among children and adults are increasing around the world and their public health relevance cannot be underestimated.[421-425] It was projected that unipolar major depression will be on the second rank on the list of global burden of disease after ischemic heart disease in 2020.[426] Strikingly, a recent study provided evidence for a link between extensive use of computers and mobile phones and depression.[97] Hence, studies about short and long-term effects of mobile phone use on mental health of children, adolescents and adults are urgently needed. A cohort study

investigating the relationship between mobile phone use and health effects in adolescents (HERMES) is currently being set up at the Swiss Tropical and Public Health Institute (SWISS TPH) in Switzerland. HERMES studies the impact of mobile phone use on psychological well-being, cognitive functions and behavior of adolescents. The study aims to recruit 800–900 8th-graders (age 13–16 years) in Central Switzerland.

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