Bundesamt
für Strahlenschutz

Ergebnisbericht

Nutzung von Mobiltelefonen und Verlauf der Gliom-Inzidenz seit 1979

Vorhaben 3618S00000 (FM 8867)

International Agency for Research on Cancer (IARC/WHO)

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Das Vorhaben wurde mit Mitteln des Bundesministeriums für Umwelt, Naturschutz, nukleare Sicherheit und Verbraucherschutz (BMUV) und im Auftrag des Bundesamtes für Strahlenschutz (BfS) durchgeführt.

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BfS-RESFOR-198/22

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urn:nbn:de:0221-2022063033222

Salzgitter, Juni 2022

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1 Summary

1.1 Introduction

In the Nordic countries, the sharp increase in the use of mobile phone occurred in the mid-1990s among adults; thus, time trends in glioma incidence rates (IR) may provide information about possible risks associated with mobile phone use. We investigated time trends in IR of glioma, and compared IR and observed number of cases to those that would be expected under a range of hypothetical mobile phone risk scenarios, encompassing risk levels reported in published case-control studies.

1.2 Methods

We analyzed age standardised IR of glioma in Denmark, Finland, Norway, and Sweden among adults 20-84 years old, using data from national cancer registries and population data covering the period 1979-2016, using a log linear joinpoint analysis. Exposure distribution of use and of high level of use were obtained from self-reported information in the Nordic Interphone, the Cosmos-Denmark and the Cosmos-France datasets. Based on analytical epidemiological studies, we considered various scenarios according to which mobile phone use would hypothetically increase the glioma risk. We quantified compatibility, or absence of compatibility between the observed data and the risk scenarios by projecting incidence rates of glioma of men aged 40-69 years old under these scenarios and comparing them with the observed incidence rates in the Nordic countries.

1.3 Results

Glioma IR increased regularly with annual percent change (APC) of 0.6 (95% confidence interval (CI) 0.4-0.7) in men and 0.3 (95%CI 0.2-0.5) in women in the period 1979-2016. There were hardly any changes in IR among men and women below age 59. In men and women in their sixties, IR increased by 0.6 (95%CI 0.4-0.9) in men and 0.4 (95%CI 0.2-0.7) in women, regularly for the whole period of observation, while IR among 70-84 years old increased very markedly, with APC of 3.1 (95%CI 2.6-3.5) among men and 2.8 (95%CI 2.3-3.3) among women over at least the last 2 decades of observation. Very few risk scenarios appeared compatible with the observed data using standardised incidence ratios analyses. The risk scenarios that appeared compatible involved either long latencies (20 years), or very low risks (RR = 1.08); in these projections, risks that would be limited to mobile phone heavy users were not compatible with the observed number of cases.

1.4 Discussion

IR time trends did not demonstrate breakpoints in their secular evolution in the last 20 years. Virtually all the reported results from the case-control studies with a positive association between mobile phone use and glioma risk were shown to be implausible in our simulations comparing them with the observed incidence rates, implying that biases and errors have likely distorted their findings; very low risks at the population level, and risks after very long latencies remained plausible. Simulations were based on high quality case registration, which is a strength, while the uncertainties in the exposure information and the limited information about some of the model's assumptions were limitations. Altogether, this study confirms and reinforces conclusions made previously, that no indications of a detectable effect of mobile phones have been found.

2 Project implementation

2.1 Work packages

Work package 1 consisted of obtaining authorizations to use data and performing a literature review.

Work package 2 consisted of extracting and preparing the data necessary for the project.

Work package 3 consisted in the evaluation of the evolution of glioma incidence rates of the adult population in four Nordic countries since 1979 to 2016 and performing statistical analyses similar to the authors' previous work (DELTOUR et al., 2012). In addition, more sophisticated statistical analyses appeared necessary in the course of the project. These sophisticated analyses have been developed and carried out, and have been reported along with the simple statistical analyses.

In the proposal for this project, three steps had been identified.

- **Step 1:** Calculation of the age-standardized incidence rates for each calendar year, including analysis of temporal trends and location of possible change points (i.e., times when the trend in incidence rates changes significantly in relation to previous years).
- **Step 2:** Prediction of the number of annually expected glioma cases assuming different risk scenarios in a simulation study. Risk scenarios have been based on the assumption of different risk estimates (percentage increase in incidence) for different exposure categories based on the duration of the call time. The risk estimates were based on values obtained in relevant studies (e.g., Interphone, CERENAT, Hardell studies). In addition, scenarios with more conservative risk estimates were also evaluated. The exposure distributions (distribution of average call duration in the population) have been extrapolated to the total population using the mobile phone usage data of the Cosmos study and the Interphone study.
- **Step 3:** The incidence trends of the simulation study were compared with the true incidence rates observed in the national populations to evaluate the plausibility of the scenario (risk estimates and exposure distribution) by means of simplified and sophisticated statistical analyses.

2.2 Collaboration

The consortium is led by the Section of Environment and Radiation, recently Environment and Lifestyle Epidemiology Branch (ENV) at the International Agency for Research on Cancer (IARC), the World Health Organization (WHO) cancer agency in Lyon, France. This is a continuation of a previous project published by Deltour et al. (2012) but with updated and more comprehensive data conducted by almost the same team. The lead is composed of Drs Joachim Schüz and Isabelle Deltour.

Participating scientists from the Nordic countries are:

- Finland - Professor Anssi Auvinen, University of Tampere and Finnish Radiation Protection Institute (STUK),
- Sweden - Professor Maria Feychting, the Institute of Environmental Medicine, Karolinska Institute,
- Denmark - Professor Christoffer Johansen and Dr Aslak Harbo Poulsen, Danish Cancer Society Research Center,
- Norway - Dr Tom Børge Johannesen, Norwegian Cancer Registry.

3 Introduction

If the radiofrequency electromagnetic field (RF EMF) exposures emitted from mobile phones during their use caused glioma, the marked increase in prevalence of use in the general population over a 20 years period would eventually result in an increase of the number of cases. This statement of an eventual increase only holds true if there is no concurrent protective factor simultaneously increasing in prevalence as mobile phone use which could diminish the incidence at the same time as mobile phone use would increase it, an unlikely situation since no such universal protective factor against glioma has so far been identified.

Before the introduction of mobile phone technology the general population had virtually no relevant RF EMF exposure to their head. Only within 20-30 years, however, almost everyone became exposed to some extent. It is known that, for situations where exposure changes would result in marked population level incidence rate changes, incidence rates (IR) time trend analysis are a strong epidemiological instrument; hence they are used to monitor population level cancer prevention interventions but have also shown to be informative in other aetiological research questions where the majority or a large portion of the cancer cases are attributable to a defined exposure (e.g., in the case of asbestos and mesothelioma (SCHONFELD, MCCORMACK, RUTHERFORD, & SCHUZ, 2014)). If there was an association, we expect that IR would increase and the time trends in these rates would demonstrate breakpoints following the changes in exposure patterns.

The populations of the Nordic countries were among the first to adopt mobile phones extensively and since 2005, have had more than 1 subscription per inhabitant on average. In these countries, high-quality nationwide and population-based cancer registries, with recording of all incident brain tumours including benign brain tumours, have been maintained since the 1950's. Hence, the analyses of these data provide excellent opportunities for surveillance studies of the occurrence of brain tumours. Glioma are the commonest type of brain tumours in adults, occurring also in the temporal and parietal lobes of the brain where exposure is highest when the phone is held to the ear; consequently, glioma is the tumour type for which the possibility to show a risk increase associated with mobile phone use has been studied most so far. Several reviews of the scientific evidence were carried out, most notably by the International Agency for Research on Cancer and by European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (BAAN et al., 2011; SCIENTIFIC COMMITTEE ON NEWLY IDENTIFIED HEALTH RISKS, 2009).

Up to 2008, the time trends of the IR of gliomas among adults in the Nordic countries did not demonstrate an increase paralleling the increasing prevalence of mobile phone use in the relevant age groups, as the IR showed no identified break in their long-term time trends, and followed their secular increase (DELTOUR et al., 2012).

Many factors affect the number of cases of a disease in cancer registries, which in general fall under one of the following categories: the prevalence of risk factors in the population, the health system and in particular the access to diagnosis, and the procedures of reporting of cases to the cancer registry (PUKKALA et al., 2018). Etiological research such as ours is primarily interested in the first category, but the latter two are known to have a potentially large impact on the rates, as evidenced for example by changes in the rates of thyroid or prostate cancer (HALL, IRISH, GROOME, & GRIFFITHS, 2014).

Changes in prevalence of risk factors, access to health care and in completeness of reporting to the registry would be reflected in the number of cases registered. Specifically, in Norway, around 2000, the registry systematized the sending of out reminders to hospitals when the administrative data (discharge or outpatient diagnosis) of the patient indicated a brain tumour (ICD-10 diagnosis of C70-

72, D32–33 or D42–43), and no other sources had data on the patient, specifically histology report, clinical report, death certificate, or radiotherapy data. In Denmark, in 1987, the reporting of cancers to the Danish Cancer Registry was changed from voluntary, with incentives, to compulsory. Diagnosis of brain tumours was also affected by improved diagnosis tools such as after the uses of computed tomography (CT) and magnetic resonance imaging (MRI) were gradually introduced. These have increased the IR of glioma, in particular among the elderly, while combined with more histopathological examinations, specific brain tumour types have risen paralleled by decreasing unspecific brain tumour diagnosis.

In some general population case-control studies conducted to evaluate the association between mobile phone and cancer, elevated odds Ratios (OR) have been reported, such as a significant 30% increase in risk for any mobile phone user, that would have increased the risk after only one year of induction period (HARDELL, CARLBERG, & HANSSON, 2011). Some experts have hypothesized that biases and other uncertainties had played an important role in these estimates (BAAN et al., 2011; SCIENTIFIC COMMITTEE ON NEWLY IDENTIFIED HEALTH RISKS, 2009), but this has not been demonstrated with certainty (FREDERIKSEN, DELTOUR, & SCHUZ, 2012; VRIJHEID, DELTOUR, KREWSKI, SANCHEZ, & CARDIS, 2006). The OR from general population case-control studies is an estimate of the rate ratio, which is the ratio of the IR in the at-risk (or exposed) subgroup of the population to the IR in the reference subgroup, i.e. not exposed subgroup (population not using mobile phones). Let us assume we were dealing with a true causal factor: an elevated OR observed in people with this exposure, compared to people without this exposure in a case control study would correspond to an elevated IR in the exposed population compared to the IR of the non–exposed population which would be elevated by a similar factor (IR among exposed people approx. equal to IR among non-exposed people times OR).

One of our goals was to evaluate the risks and induction periods that would yield detectable increases in the incidence rates in an hypothetical population of the same size and structure as that of the Nordic countries; or conversely, if no increases in secular trends were detectable in the observed incidence rates, the levels of risk and induction periods which could be excluded, assuming that no other etiological factor than the prevalence of mobile phones had been modified.

The aims of our project were first to identify secular time trend changes. We analyzed the time trends in the incidence rates of glioma among adults aged 20 to 84 years of the Nordic countries from 1979 to 2016 (step 1 of the work description). Then, we addressed the question whether the observed time trends and observed number of cases were statistically different from the one we would observe if we assumed that the use of mobile phones caused glioma, so if we assumed that there was a true causal association (step 2 and step 3 of the work description). Within this, we delineated the levels of risks and the duration of induction periods that would not be compatible with the observed time trends and numbers of cases in this population (step 3 of the work description). We also discussed these findings in light of some of the elevated OR found in the literature. The study tested the consistency between risks that have been reported and the effect they would have had at the level of the population, had they been true. Noteworthy, the study was not meant to dismiss every single hypothetical association, as it would most likely always be possible to devise a pattern of risk that would fit the data. The study also provided an outlook for future studies by informing which magnitude of risk would not be plausible.

4 Epidemiological literature review

Due to the widespread exposure to mobile telephony and the concern that radio-frequency electromagnetic fields might pose a health risk, research is actively ongoing in this field. The

association between mobile phone use and glioma or malignant brain tumours has been investigated in cohort studies and in case-control studies. Here we report on these studies conducted on adults published in the last 15 years, on glioma or malignant brain cancers. For clarity of presentation, the other incidence studies are discussed together with the results of this one in the discussion section.

4.1 Cohort studies

Associations have been investigated in several large cohorts (BENSON et al., 2013; FREI et al., 2011). Generally, a cohort study with exposure information collected prior to disease occurrence or independently of study subjects is regarded as the best study design, as it minimizes differential exposure misclassification, i.e., misclassification that is dependent on the disease and can lead to biased risk estimates. In this study design, since the exposure information is collected prior or independently of the disease, recall bias is not a concern. In studies of rare outcomes, however, very large cohorts are required, which can limit the possibility to collect very detailed exposure information and history. Further, the correlation between exposure to RF fields and the use of various applications may be low to moderate. Therefore, non-differential exposure misclassification can be a problem in cohort studies. Non-differential exposure misclassification can dilute risk estimates, should a true effect exist, and makes it difficult to detect modest risk increases. Cohort studies did not report increased risks.

One of the main cohort studies was a nationwide study conducted in Denmark on all Danes aged >= 30 years and born after 1925, with follow up over the period 1990-2007. The analysis compared IR among the early private subscribers of mobile phones (up to 1995) with the rest of the adult Danish population. No associations were seen: incidence rate ratios of glioma were 1.04 (95%CI 0.85 -1.26) in men and 1.04 (95%CI 0.56-1.95) in women when comparing persons holding a subscription in their own name since 10 years or more to non-subscribers (FREI et al., 2011). No significant increase for any type of brain tumour was either observed among the longest term subscribers of 13 years or longer. Information on early private subscription was obtained from mobile phone records, therefore was complete and not subject to individual recall error, but misclassification of exposure status could occur, since holders of companies' phones were included among non-users, and it could occur that the subscriber was not the sole or main user. The other main cohort study was the UK Million Women study, in which exposure to mobile phone was assessed among 792,000 women with 2 questions, the information was therefore self-reported, and occurrence of cancers and central nervous system tumours obtained from the UK National Health Service (NHS). This study included women born between 1935 and 1950, recruited through 66 NHS breast screening centres in England and Scotland in 1996-2001. There was no association for any type of brain tumour in relation with years since first mobile phone use or among those using mobile phones on a daily basis. The relative risk (RR) for glioma was 0.78 (95%CI 0.55-1.1) for women using a phone since 10 years or more compared to the rest of the study population (BENSON et al., 2013). Advantages of these cohort studies were the prospective nature and the large representative (or even nationwide) samples, while the disadvantages were that only crude exposure information was collected, leading to an inability to specifically investigate the most intense mobile phone users. The Europe-wide prospective COSMOS cohort (with IARC participation) is specifically focused on the association between mobile telephone and health outcomes. It counters the limitation of the imprecise exposure assessment in other cohorts by recording the network operators' official usage data (SCHUZ et al., 2011; TOLEDANO et al., 2018). However, results of the COSMOS study are not expected in the near future.

4.2 Case-control studies

The detailed exposure assessment was an advantage of the case-control studies, which on the other hand suffered from recall and selection bias as has been sufficiently documented (ROOSLI, LAGORIO, SCHOEMAKER, SCHUZ, & FEYCHTING, 2019). Selection bias occurs when participation in the study is low and different for cases and controls. In the mobile phone context, this could occur, for example, when fewer non-users controls participate than initially randomized, while participation rate among cases is uniformly high, regardless of mobile phone use. Recall bias would occur when control subjects forget about their distant exposures such as their first mobile phone used, while cases make more effort to provide accurate description of their exposures. Associations might be amplified or even entirely created due to the presence of these biases in a specific study. The risk of glioma in adult general population has been investigated in several case-control studies in relation to mobile phone use or to RF-EMF emitted by mobile phones.

The largest study was the international Interphone case-control study (N=2708 glioma cases, 2972 matched controls) which overall showed an inverse association of glioma risk with mobile phone use (odds-ratio (OR)=0.81 95%CI 0.70-0.94), which was considered biologically improbable and therefore mostly attributed to selection bias related to low response rates among participants. Odds Ratios of glioma, 10 or more years after first use of mobile phone, was 0.98 (95%CI 0.76-1.26), but the OR was elevated for the group of the 10% highest users (OR=1.40 95%CI 1.03-1.89 comparing users who had accumulated at least 1640 hours of lifetime use to non-users). This group corresponds to about 5% of the entire study population of 30-59 years old (INTERPHONE STUDY, 2010) (Table 1**Error! Reference source not found.**). Analyses derived from the Canadian subset of the Interphone study, also reported elevated risks for subjects who had accumulated 558 lifetime hours of use or more (OR =2.0, 95%CI 1.2 - 3.4), (MOMOLI et al., 2017).

An entirely different team conducted a series of case-control studies on malignant brain tumours in Sweden following the same methodology. In its most recent pooled publication of 2015, it included a sizable number of cases (N=1498) and 3430 controls. The analysis showed elevated ORs of gliomas for all durations of mobile phone use (HARDELL & CARLBERG, 2015). For example, the OR for malignant brain tumours was 1.4 (95%CI 1.1-1.9) 10 to 15 years after first using a mobile phone, and use of mobile phones more than one year produced an OR of 1.3 (95%CI 1.1-1.6).

A more recent general population case-control study conducted in France (CERENAT) (N=253 gliomas cases and N= 892 matched controls), which had much smaller sample size than the other two, showed non significantly increased OR (1.24, 95%CI 0.86 - 1.77) for ever use of mobile phone in the adult population, and the OR was significantly elevated for the heaviest users of mobile phone: in that dataset, subjects who reported more than ≥896 hours of lifetime use had an OR of 2.89 (95% CI 1.41 - 5.93) compared to non-users, and a non-significantly elevated OR of 1.78 (95%CI 0.98-3.24) for 339 hours of use or more was observed (Table 1). It also showed an OR of 1.61 (95%CI 0.85 - 3.09) comparing users for 10 years or more to non-users (COUREAU et al., 2014). A small pilot study conducted in France in 2005 reported an OR of malignant brain tumours of 1.07 (95% CI 0.41 - 2.82) for the highest category of lifetime use analyzed, based on 116 cases and 116 controls in total in the study (SPINELLI et al., 2010). The authors developed a unique categorisation of mobile phone use, which was similar to the pack-year categorisation used in smoking analyses, such that the duration of mobile phone monthly subscription was multiplied by the number of years of subscriptions.

Another study conducted in Korea (N=285 glioma cases, 285 controls) reported an OR of 1.04 (95%CI 0.52 - 2.09) for more than 7 years of mobile phone use (YOON et al., 2015). Case-control studies, however, are prone to recall bias when exposure information is self-reported from the study participants, whereby cases might report their exposure differently than controls (e.g. with more

details). Recall bias may generate spuriously elevated associations between exposure and disease. Validation studies comparing self-reported mobile phone use with objective data from network operators showed generally large errors. They also showed that recall accuracy appeared to deteriorate over time, with a tendency to overestimation of high use and underestimation of low use, and differences between cases and controls (AYDIN et al., 2011; KIYOHARA et al., 2016; PETTERSSON, BOTTAI, MATHIESEN, PROCHAZKA, & FEYCHTING, 2015; TOLEDANO et al., 2018).

Re-iterating our second aim to delineate the levels of risks and the duration of induction periods that would not be compatible with the observed time trends and numbers of cases, we used a selection of elevated risks observed in the studies above (from the IARC Monograph, Baan et al. 2011), irrespective of study quality and plausibility of the results, to check their consistency with the factual observed time trends (Table 1).

5 Material

5.1 Data

Numbers of primary gliomas in patients aged 20 to 84 years at diagnosis and diagnosed between 1979 and 2016, were obtained from the national cancer registries of Denmark (Danish Cancer Registry), Finland (Finish Cancer Registry) , Norway (Cancer Registry of Norway) and Sweden (Swedish Cancer Registry)[Retrieved 22/01/2021]. We included only primary cancers (to exclude secondary effects by other tumour), and we collected nationwide data from each participating country.

The age cutoff of 84 years old has been chosen to explore the possible decrease in the completeness of ascertainment of patients of this age group in the registries, while retaining some comparability with the previous analysis (DELTOUR et al., 2012). The lack of completeness has been studied in the framework of the Swedish cancer registry. Barlow and colleagues showed that in 1998, while the under-reporting of nervous system tumours for cases under age 70 was 6% in men and 7% in women, it was 44% in male cases 70 or older, and 30% in female cases 70 years and older (BARLOW, WESTERGREN, HOLMBERG, & TALBACK, 2008). Further work on the completeness of the Swedish cancer registry has been carried out (TETTAMANTI et al., 2019). It was relevant to evaluate if in the more recent years, the incidence rates among the elderly people showed changes that could be compatible with diagnosis and registration improvements in these countries. Sizes of population at-risk by 5-year age groups were acquired from the national population registers for each calendar year.

5.2 Outcomes selection

We included all gliomas combined defined according to the International Classification of Disease for Oncology version 3, located in the anatomical zone C71 (brain), and with morphological codes between 938 and 946, and similar codes in the International Classification of Disease version 7 for the early period. In Deltour et al., 2012, we had considered only the group of all gliomas defined as tumours located in the brain (topography C71), and morphologies 938-948 (i.e., glioma as a broad group when considering the ICD-O-3 classification). However, this group includes embryonal tumours, which rarely occur in adults, and which are thought of as of embryonal origin. Therefore, for this analysis, we defined our group of glioma, without including these tumours of embryonal origin (i.e, the medulloblastoma - codes 9470-9480), which represent < 1% of adult intracranial tumours (LOUIS et al., 2016). We also restricted to tumours of the glial tissue only, excluding neuronal and mixed neuronal-glial tumours. We excluded any diagnosis coded as 9412 since this code corresponds to the desmoplastic infantile astrocytoma and ganglioglioma, and it mainly occurs

in infants typically <20 months. We also excluded any diagnosis coded as 9413, which are dysembryoplastic neuroepithelial tumours, because these were also neuronal-glial tumours; 75% of these tumours are diagnosed before age 20 (LOUIS et al., 2016). Other codes referring to neuronal and mixed neuronal-glial tumours (9492, 9493, …) were outside the range of code for glioma (938-948) (Annex Table 1). The primary analyses are performed on all gliomas combined to adjust for shifts in incidence reporting rates of the subgroups, for example glioblastomas.

Separate analyses were produced for glioblastomas, all high grade gliomas, all low grade gliomas (See Annex Table 1 for the list of topographical and morphological codes).

5.3 Exposure distributions

Our simulations made use of age and sex specific exposure distributions, information which is not readily available. To obtain these distributions, we used data from the large international case control study Interphone (CARDIS et al., 2007) and from the large prospective cohort study Cosmos (SCHUZ et al., 2011). Indeed, the questionnaires of these two studies collected lifetime exposure histories from their participants, permitting the abstraction of the adequate age-sex-specific exposure distributions, and the questionnaires used the same definition of mobile phone users, i.e. people who used a mobile phone on average at least once a week over a period of at least 6 months. For simplicity, these were called users of mobile phone in the remainder of the document. Within Cosmos, we used Denmark and France to represent countries with an early widespread use of mobile phones and one where this widespread use occurred much later, by this capturing the variety across countries. Each of these 3 exposure distributions were used in the simulations.

Exposure distribution from Nordic Interphone dataset: The prevalence and amount of use of mobile phones were obtained from self-reported information in a sample of the general population of the Nordic countries interviewed for the Interphone study, i.e. the controls (aged 18-69 years at interview) (INTERPHONE STUDY, 2010). The data collection (period during which subjects were interviewed about their lifetime use of mobile phone for the Interphone study) occurred between 2000 and 2002-2003 in Denmark, Finland, Norway and Sweden. From the Interphone dataset restricted to these countries, we abstracted the proportion of men aged 40-59 years old (and 60-69 years old, respectively) who used mobile phones in each calendar year of the period 1980 to 2002, (for example, considering the year 1998, we abstracted the proportion of men 40-59 years old in 1998, who used their phone in 1998; by repeating this for all calendar years, we obtained the evolution of the proportion of users in men aged 40-59 years over time). We also abstracted the phone use each 5, 10, 15, and 20 years before the calendar year (for example, considering the men aged 40-59 in year 1998, we abstracted their phone use in 1993 for the 5 year lag, 1988 for the 10 year lag, 1983 for the 15 year lag and 1978 for the 20 year lag). We also abstracted the proportion of people qualifying as heavy users, in any given calendar year among men aged 40-59 years old that year. We used 4 definitions of “heavy use”, which were all subgroups of the user group with no lag: those who had accumulated at least 1640 hours of conversation time in their life, at least 896 hours of call time, at least 558 hours of call time and at least 339 hours of call time. For the period 2003-2016, we extrapolated the use in 2002 with a linear increase, which slowed down in the later years (OFFICIAL STATISTICS OF FINLAND, 2007; TELESTYRELSEN et al., 2010; TELESTYRELSEN et al., 2011). The structure of the dataset did not permit to obtain information on the use of mobile phone in the distant past for men aged 60-69 years old.

Exposure distribution from the Danish Cosmos dataset: The prevalence and amount of use of mobile phones were obtained from self-reported information in a sample of subscription holders in Denmark aged 20-69 years old at recruitment interviewed for the Cosmos study in 2007 and 2009 (N=25,907) (SCHUZ et al., 2011; TOLEDANO et al., 2018). Although mobile telephone operator data is

collected prospectively for some participants of the Cosmos study, this data was not available retrospectively, i.e. before the inclusion of participants in the cohort, period during which only self-reported information was available. We abstracted for men aged 40-59 years old (respectively 60-69 years old), the proportion of those who used mobile phones in 1987, 1990, 1995, 2000, 2005, and at interview, which allowed to compute the prevalence of use by linear interpolation between these time points between 1987 and 2009. We repeated the same 5, 10, 15 and 20 years before each calendar year. We abstracted the proportion of heavy users in the same years, with the same 4 definitions of "heavy use" as described for the Nordic Interphone dataset. In the Cosmos questionnaire, responses were elicited using categorical answers (including 30-59 min / week, 1-3 hours / week, 4-6 hours /week, >6 hours/week). For this reason, only approximate definition of heavy users could be abstracted and conservative assumptions were used. We assumed that on average, subjects kept the same use between data points and we used the midpoint of the interval as representative of the interval's range of values. For example, subjects who reported that they used their phone 1-3 hours per week in 2000, were, by the end of 2002, in the group of people who had accumulated 339 hours of use or more. This was calculated by taking the midpoint of the interval (2.5 hours) times 52 weeks per year times 3 years, i.e. 390 hours. For the period 2010-2016, we extrapolated the use in 2009 with an annual increase which was slightly slower than that observed in the last years of observations.

We abstracted the same information for 60-69 years old. In Denmark, subjects were included if they were 18-69 years old. Due to the age structure of the dataset, there was little or no data to estimate the prevalence of use among 60-69 years old in the distant past. For the distant past prevalences, we relied on data from the 40-59 years old weighted with adjustment factors, computed on the years for which both 60-69 years old and 40-59 years old prevalences were available.

Exposure distribution from the French Cosmos dataset: The prevalence and amount of use of mobile phones were obtained from self-reported information in a sample of the general population of France interviewed for the Cosmos study in 2019, using the same methods as in Denmark (N= 9,647).

5.4 Ethical approval

The IARC Ethics committee approved the study (reference 15-39). In Denmark, the Data Protection Agency approved the project. In Finland, the study received permission from the National Institute for Health and Welfare. In Norway, de-identified data where no link is made with other registries do not need ethical approval, and the project was approved by the Data Delivery Unit at the Cancer Registry of Norway. The Swedish data were anonymous, and therefore not personal data; thus, ethical permission was not required.

6 Statistical methods

First we described the observed IR. Second, we analyzed if the observed number of cases were compatible with scenarios of mobile phone related increased risks. We analyzed this second question using two population subgroups, namely men aged 40 to 59 years, and men aged 60-69 years old with several statistical models and perspectives. Fewer women than men owned a mobile phone in the early days of mobile telephony, in Norway and in Denmark as in the other Nordic countries, and therefore the analysis of the female population groups would have had lower statistical power to detect risk increases than the analysis of the male data (https://www.ssb.no/a/publikasjoner/pdf/sa51/kap20.pdf) (SCHUZ, WALDEMAR, OLSEN, & JOHANSEN, 2009). Men aged 40 to 59 years aligned well with the international protocol of the Interphone study which included cases diagnosed between 30 and 59 years old, easing comparison

with results obtained from these data (Table 1). We also conducted these analyses in men aged 60-69 years old. Men aged 60-69 years in 2015, were 35-44 in 1990, the population group that started first to use mobile phones in the early years of mobile telephony. It was therefore of interest to examine the trends in both population groups.

6.1 Observed incidence rates and statistical modelling of cases numbers and rates

Annual age-standardized IR of gliomas per 100,000 person-years were calculated separately for men and women, standardized to the European standard population (WATERHOUSE, 1977), and truncated to the age groups 20-84. We described the combined age range (20–84 years) and the age groups 20–39, 40–59, 60–69, and 70-84 years; country-specific and combined data were analyzed for the period 1979-2016.

In line with models of cancer occurrence used elsewhere (PARKIN, WHELAN, FERLAY, & STORM, 2005), we used the Poisson distribution to analyse the observed number of cases, for the whole population or in any gender-age or tumour type subgroup considered. All the analyses described below used the Poisson distribution to model the occurrence of cases, except when otherwise specified. We used simple, generic, and more complex models of the Poisson parameter. In its simplest form, this model had person-years and incidence rate per unit person-time as parameters. Equation (1) described this simplified model:

$$O_i \sim \text{Poisson}(b_i * PY_i), \qquad (1)$$

where O denotes the observed number of cases, i the calendar year (1979 to 2016), b the incidence rate, and PY the number of person years.

The Poisson distributional assumption was tested. The test of the adequacy of the Poisson model to the data was performed by fitting a more general model (i.e. the negative binomial model, which encompasses the Poisson model as a special case) to the data, and testing if the general model could be simplified into the Poisson special case. We also evaluated the goodness of fit of the Poisson model to the data. When the negative binomial model and when the Poisson model were fit, population and time were included as covariates. In the male and female age subgroups 20-39, 40–59, 60–69 years old, which were the subgroups in which the best fitting model from the joinpoint analyses did not show trend changes, the tests of the alpha parameter estimate from the negative binomial regression showed that none of these hypotheses were rejected at the 5% significance level, showing a good fit of the Poisson model; this was confirmed by the goodness of fit tests of the Poisson model in all these situations (data not shown), thereby justifying the use of Poisson distributions in the statistical modelling.

A piecewise log-linear model called joinpoint analysis (Joinpoint Regression Program, version 4.8.0.1 – April 2020; Statistical Research and Applications Branch, National Cancer Institute), without constraints on the positions of the nodes or joinpoints was used to identify trend changes and to estimate annual percent change in incidence rates over the period 1979–2016. The model was specified to include a maximum of 3 joinpoints, which could occur in the middle of a year or between two consecutive years. The model constrained the joinpoints to be at least a year and a half from each other, and at least two years away from the start and end of the study period. Here, we used the Poisson distribution to model the number of cases (equation 1), implying heteroscedasticity i.e. the variance is not constant over time. Under the assumption of heteroscedasticity and uncorrelated errors, the best-fitting model was searched on 4499 randomly permuted datasets using the grid search method. Tests, at an overall two-sided significance level of 0.05, were not adjusted for

autocorrelation since uncorrelated errors were assumed. Of note, when the best fitting model has no joinpoint, the model of the IR is:

$$\text{Log } b_i = a_0 + a_1 * (i-1979), \qquad (2)$$

where b is the incidence rate, i indicates the calendar year and a_0, a_1 are the parameters estimated by the model.

6.2 Statistical modelling of the incidence rates in relation to the mobile phone hypothetical risk

The sum of two Poisson-distributed independent random variables follows a Poisson distribution. Therefore, the observed number of cases can be conceptualized as resulting from two distinct subsets: the cases originating in the "not-at-risk" population (e.g., people not using mobile phones), and the cases originating in the "at-risk" population (e.g., people using mobile phones). We have developed a variety of hypothetical risk scenarios around this concept.

The following equation describes the generic model of the simulations:

$$O_i \sim \text{Poisson}(b_i * RR^J * E^J_i + b_i * N^J_i), \qquad (3)$$

where O denotes the observed number of cases, i the calendar year (1979 to 2016), b the baseline IR (the incidence rate in the not-at-risk population), RR the relative risk (e.g. the risk of glioma of specific mobile phones users divided by the risk of persons not using mobile phones), J the index of the hypothetical risk scenario, which combines a presumed induction period and a specific risk group, E the number of persons at risk (depending on the scenario, this was either all users with one of the induction periods or one of the subgroups of heavy users), and N the number of persons not-at-risk (the remainder of the population, which depended on the scenario). The following equation constraints the person-years:

$$PY_i = N^J_i + E^J_i, \text{ for any year i and any scenario J,} \quad (4)$$

using the same notations as before.

Therefore, our model (3) stated that the number of cases was a sample from a Poisson distribution, in a population of the same size as the population of the Nordic countries with the same prevalence of use, with a baseline incidence rate for not-at-risk subjects and a rate for exposed/at-risk subjects. It should be noted that this model cannot be estimated without additional assumptions, since it has too many unknown parameters (namely all the b_i and the RR).

6.2.1 Scenarios of hypothetical mobile phone risk

In our core hypothetical scenarios of risk, we assumed that the use of mobile phones increased the risk of glioma after an apparent induction period during which no increase occurred. Each scenario combined an induction period (0, 5, 10, 15 and 20 years) with a value of RR which was either estimated from the model fit (paragraph 6.2.2 and 6.2.3), or fixed within a range of values (1.05, 1.08, 1.1, 1.2, 1.3, 1.4, 1.5, 2, 2.5) (paragraphs 6.2.4), that multiplied the baseline incidence rate for all mobile phone users. We also ran scenarios in which only heavy users were at risk, with 4 definitions of heavy users: those who had accumulated >= 339 hours, >= 558 hours, >= 896 hours or >=1640 hours of mobile phone conversation time over their lifetime. The values of relative risks were chosen according to the elevated risks reported in the literature (Table 1). We also developed a scenario of risk in which we hypothesized that the risk group was restricted to people using the Global System for Mobile Communications (GSM) intensively, so the size of that group would not increase after the introduction of Universal Mobile Telecommunications System (UMTS) network (2003). Long Term Evolution (LTE) network was considered as conferring similarly low exposure as

UMTS, compared to GSM network in this scenario. Distributions of the sizes of these groups at risk were abstracted from 3 sources (the Interphone study, the Cosmos study in Denmark, the Cosmos study in France) to cover a range of possible exposure distributions. A schematic description of the scenarios considered is provided in Table 10 and Table 11.

6.2.2 Simplified statistical model of the number of cases and the IR

To gain more insight into the data, we performed analyses of the observed number of glioma cases, according to a simplified version of the generic model (3). As described previously, we assumed that the number of cases was distributed according to Poisson random variables, and the following equation describes our simplified model:

$$O_i \sim \text{Poisson}(b * N^J_i + b * RR * E^J_i), \qquad (5)$$

using the same notations as in model (3). The difference between model (3) and model (5) was that the baseline incidence rate b was constant in the simplified model (5) over the whole observation period. The sizes of the exposed (E) and not exposed (N) subgroups were described in Equation (4). Fitting this model to the data allowed to estimate jointly b and RR. We reported the estimated RR based on the observed data, and conditional on the exposure distributions, while the incidence rate b was estimated, but not reported. In line with the analysis published previously (DELTOUR et al., 2012), this model implicitly assumes that all the modifications in incidence would be explained by mobile phone related risk, exclusively. For each dataset of observed number of cases, we estimated the relative risk (RR) under the Poisson model, with known at-risk and not-at-risk populations (E and N), based on the exposure distribution and total size of at-risk population. Because the likelihood of model (5) could not be mathematically expressed as a standard Poisson regression model, we obtained the estimates of the parameters with a maximum likelihood procedure (ml function of Stata, StataCorp. 2007. Stata Statistical Software: release 14.2. College Station, TX: StataCorp LP).

6.2.3 Estimation of the power of the simplified model

We computed the power of the dataset to detect a risk if there was a true risk increase to be detected, similarly to previous research (DELTOUR et al, 2012). For each scenario described in paragraph “Scenarios of hypothetical mobile phone risk”, we sampled the number of cases according to model (5), conditional on the sizes of at-risk and not-at-risk groups for this scenario, and a constant baseline rate. For males 40-59 years old, a baseline rate of 8.1 cases per 100,000 person-years at risk was used, this was the incidence rate of glioma observed in the year 1979 in all countries combined, among men aged 40-59 years. We analyzed 1,000 simulated datasets per scenario, based on the stability of the estimates. For each simulated dataset, we estimated the relative risk (RR) under the Poisson model, with known at-risk and not-at-risk populations (E and N), from the Nordic Interphone Dataset, from Cosmos-Denmark and from Cosmos-France. Because the likelihood of model (5) was not standard, we obtained the estimates of the parameters with a maximum likelihood procedure. Out of the 1,000 estimates, the proportion of lower bounds of the 95%CI above 1.0 was an estimate of the power of the study; i.e. demonstrating a significantly increased RR, conditional on the scenario.

6.2.4 Sophisticated statistical model of the IR and analysis using Standardized Incidence Ratios

The analysis described in the paragraphs „Simplified statistical models of the IR“ and „Estimation of the power of the simplified model“ had limitations because it used the assumption that the baseline incidence rate would be constant throughout the period of observation, should RF-EMF exposure from mobile phone use have no impact on glioma rates. However, previous analyses (DELTOUR et al., 2012) have shown that rates of glioma among the elderly increased regularly, somewhat in

contradiction with the assumption in these simplified models for the men aged 60-69, while the increase was very small and not significant among 40-59 years old men. Specifically, rates have been shown to be increasing among men aged 60-79 years old by 0.9% per year until 2008 in the Nordic countries (DELTOUR et al., 2012). Prior analyses also tended to indicate that mobile phone related risk, should it exist, would be small. Therefore it could be inferred that other factors, for example related to registration of cancer cases or improved accessibility to improved diagnostic tools, were playing a role over the period of observation, especially for older people. To mimic reality better in our statistical modelling of the data, we developed a second set of analyses, whose models were more flexible in the sense that they permitted to include the presence of other factors in the model, together with the estimation of a possible mobile phone related risk. These other factors, which were not explicitly specified in this statistical modelling, would encompass the role of improved registration, improved accessibility to improved diagnostic tools, and other factors influencing the ultimate registration of the glioma cases in the cancer registries.

To this aim, we developed an alternative method to analyse the data, based on the calculation of Standardised Incidence Ratios (SIR), comparing the observed number of cases with the expected number of cases in a population of the same size and age structure, for the calendar years of follow-up.

$$\mathrm{SIR}^{\mathrm{J}} = \frac{\sum_{\mathrm{i}} \mathrm{O}_{\mathrm{i}}^{\mathrm{J}}}{\sum_{\mathrm{i}} \mathrm{Expected}_{\mathrm{i}}^{\mathrm{J}}}$$

The 95% CI of the ratio of observed to expected cases has been derived, using the relationship between the Poisson distribution and the chi-square distribution (https://seer.cancer.gov/seerstat/WebHelp/Standardized_Incidence_Ratio_and_Confidence_Limits.htm). The calculation of the expected number of cases under the same various scenarios of risk (Table 10Table 11) is described in the following paragraph.

In this analysis, the evolution over time (indexed by i) of the underlying incidence rate b_i due to unknown, unmeasured factors, was modelled according to a linear increase,

$$\mathrm{Log}\ b_i = a_0 + a'_1 * (i\text{-}1979), \qquad (6)$$

using the same parametrization as in the joinpoint analysis in paragraph 6.1.

In this SIR analysis, building on the results of the joinpoint analyses carried out in 6.1 (model 1 and 2), our model of b_i (6) was that a'_1 was half the value of a_1 estimated in the joinpoint analyses; a_0 was unchanged [$\mathrm{Log}\ b_i = a_0 + 0.5*a_1 * (i\text{-}1979)$, with a_0 and a_1 estimated from the joinpoint analyses]. In order to fit models that were closer to the observations, and still allow flexibility to estimate an hypothetical mobile phone related risk, these analyses assumed that half of the total observed increase in the age and sex group estimated with the joinpoint model was attributed to factors other than mobile phones, for example improved accessibility to improved diagnostic tools, while our interest focused on estimating if the other half of the increase in incidence could be explained by mobile phone – associated risk and exposure data.

The expected number of cases in this age group in year i, for scenario J was computed according to:

$$\mathrm{Expected}^{\mathrm{J}}_{\mathrm{i}} = b_i * \mathrm{RR}^{\mathrm{J}} * \mathrm{E}^{\mathrm{J}}_{\mathrm{i}} + b_i * \mathrm{N}^{\mathrm{J}}_{\mathrm{i}}. \qquad (7)$$

Formula (7) is in line with model (3), with, as before, i indexing the calendar year, RR the relative risk, E the size of the at-risk group, N the size of the not-at-risk group, and b_i from (6).

The proportion of the observed increases that would be attributable to mobile phones, is unknown and to evaluate the sensitivity of the results to the model's assumptions, we ran analyses with the alternative model in which one quarter of the increase could be explained by mobile phone related

factors, while three quarters of the increases were assumed to be related to other factors influencing glioma case registration [Log $b_i = a_0 + 0.75*a_1 * (i-1979)$ with a_0 and a_1 from the joinpoint analyses].

The interpretation of these analyses was that if the confidence interval of the SIR did not include 1, the observed number of cases was statistically different from the one that would be expected, if the scenario of risk, the induction period, the exposure distribution, and fraction of baseline rate explained by mobile phones had been correct. Conversely, if the CI included 1, the observed number of cases was not statistically different from the one that would be expected, if the scenario of risk, the induction period, the exposure distribution, and fraction of baseline rate explained by mobile phones were correct, providing support for that specific risk scenario. We applied this SIR analysis separately to men aged 40-59 years old, and to men aged 60-69 years old, and discussed the results of these sets of analyses together.

7 Results

7.1 Glioma incidence trends

This study was based on 28,015 male and 20,630 female glioma cases diagnosed from 1979 to 2016 in Denmark, Finland, Norway and Sweden (called “the Nordic countries” in the following). In 2016, the number of glioma cases was 1,724 in a population of 19.7 million adults aged 20–84 years. Over the last 10 years of data, Sweden accounted for 38% of the population and of the cases; of the remainder, Denmark, Finland, and Norway had populations of similar size. The age-standardized incidence rates were higher in men (9.1 per 100000 person years) than in women (6.1 per 100 000 person years), and higher with increasing age. All countries had comparable rates; Norway had slightly higher rates, while Finland had slightly lower rates in both sexes (Table 2 and Table 3).

Joinpoint analyses described in paragraph 6.1 showed that overall, the trends were smooth: glioma rates increased by 0.6% (95% CI 0.4%-0.7%) per year in men and 0.3% (95% CI 0.2%-0.5%) per year in women over the period 1979-2016 in the Nordic countries combined (Table 4 and Table 5), and in each country separately except for a marked increase in 1979-1984 in Swedish men (APC about 6%). For the younger age groups (20-39 and 40-59 years old), the time trends were smooth and did not demonstrate strong increases at any point in time during the period 1979 to 2016 in any country among men (Table 6), and women (Table 7). Below the age of 60, incidence rates were generally stable over the whole period (Figure 1, Table 6 and Table 7). Among people aged 60-69 years old, incidence rates increased gradually by 0.6% in men and 0.4% in women per year, and these regular increases with no joinpoint were observed in every country and at a very similar rate in both sexes, except among Swedish women, whose rates showed a slight decrease. Irregular patterns were observed among the persons aged 70-84 years old at the beginning of the observation period, while for at least the last 12 years of observation, all countries showed highly increasing rates. Exceptions to this general pattern were noted among the Finnish males and the Norwegian females, in which an increase was seen at the beginning of the observation period that lasted at least 21 years.

The analysis by subgroups of tumour types could be performed only for the period 1990-2016 for reasons of data availability: in Sweden, a separate code for glioblastoma did not exist prior to 1993, and very few of the tumours which had been diagnosed during the period 1990-1992 were retrospectively coded into this code. Indeed, cancer registries are continuously updated when additional information becomes available on an earlier diagnosis, for example.

Among men and women, the rates of glioblastomas increased in the last years of observations, while the rate of other high-grade gliomas decreased (Table 8 and Table 9). Rates of low grade gliomas

were relatively stable in all countries since the mid 1990's except in Denmark, where substantial increases were noted towards the end of the period of observation, albeit non-significant.

7.2 Description of mobile phone use levels among 40-69 year old men

We analyzed the prevalence of use in 2 population subgroups and in 3 datasets (Interphone, Cosmos-Denmark or Cosmos-France). Depending on the source of information, the self-reported prevalence of use or of heavy use of mobile phone varied (Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7).

Among men 40-59 years old, the prevalence of users was highest in the Danish Cosmos dataset, intermediate in the Interphone dataset, and lowest in the Cosmos-France dataset, except in the period 1979-1989, period during which the prevalence was very low or nil in all datasets. In the Interphone dataset, the self-reported prevalence of ever use ranged from 2.4% in 1980, which was the earliest year on which data was collected in the Interphone questionnaire, to 79.4% in 2002, extrapolated to 96% in 2016. Compared to the Cosmos-Denmark dataset, the largest difference was in 1987, a moment at which 19 % of the sample of men 40-59 years old at the time reported talking on a mobile phone, while in the Interphone questionnaire, only 5 % of men reported using one at that time. In the Cosmos-Denmark dataset, this proportion of users was reduced to 13% when people reporting talking less than 5 min/week were considered non users (data not shown). A similar situation is observed in the French dataset, where mobile phone use reached the level reported in Denmark with a 5-7 years delay.

When the prevalence of cumulative lifetime use to any level of use (>= 339 hrs, >= 558 hrs, >= 896 hrs, >= 1640 hrs) were considered, Interphone participants reported the highest prevalence of having reached that level of use, while Cosmos-Denmark participants reported somewhat lower levels. Cosmos-France participants also had the lowest level of accumulated use at any given point in time. When exposure was limited to the period before UMTS existed (2003), the proportion of men aged 40-59 who had reached that level of use was the same or very similar in the Cosmos datasets (8% versus 8% and 11% versus 15%). Of note, when prevalences were abstracted from the Cosmos-Denmark and the Cosmos-France datasets, they exhibited wavelike increases, due to the categorical variables used in the questionnaire, and the conservative treatment of the data.

The difference between Cosmos-Denmark and Cosmos-France was roughly 6 years to reach the same level of use, when prevalences were higher than 20%.

Among men 60-69 years old, prevalences of use were lower than those among men 40-59 years old (Figure 7). The highest prevalences were obtained on the Cosmos-Denmark dataset, while the lowest prevalences were in the Nordic Interphone dataset. These numbers were also less accurately registered, because all 3 studies had small sample sizes in this age range at recruitment, and data had to be extrapolated for the distant past in this age range.

Therefore using these 3 sets of exposure prevalences could give us a range of possible exposure distributions in the population.

7.3 Estimated relative risks using the simplified statistical modelling of the observed number of cases

When the simplified statistical models were adjusted to the observed number of cases in men aged 40-59 and in men aged 60-69 years old, assuming the at-risk group of appropriate size and the exposure distributions of Nordic Interphone, Cosmos-Denmark and Cosmos-France studies, estimates of the relative risks (RR) and their 95% CI were obtained (Methods paragraph 6.2.3, results Table 12 and Table 13, Figure 8, and Figure 9). Specifically these numbers should be interpreted as

follows, 1.07, 95%CI (1.01; 1.12) (Table 12, row 2, columns a) were the RR estimate and 95%CI estimated when the model was fitted to the observed number of cases in men 40-59 years old, when the at-risk group was assumed to be all users after the 5 years of induction period, the exposure prevalence was estimated based on the Nordic Interphone controls, and the baseline rate for not at-risk group was assumed to be constant over the 38 years of observation. Among men aged 40-59 years old, the estimated RRs were around 1.06 for all induction periods irrespective of the source of the exposure distribution (Interphone, Cosmos-Denmark or Cosmos-France) and the induction period considered (0, 5, 10 15 or 20 years), when all users were considered at risk. In Table 13, estimates were obtained based on data of men aged 60-69 years old, and Figure 8 and Figure 9 present the same results graphically, combining the 2 age groups. Among men aged 60-69 years old, these estimates ranged between 1.21 and 1.54. Although most of the estimates in the analyses of 40-59 and 60-69 years old men were statistically significantly different from 1.0, they were hardly ever compatible between each other. Only for the longest induction period considered (20 years) did the confidence intervals of the two age group present a borderline overlap at the value of 1.31, for the Cosmos-France exposure distribution. When high users were considered at risk, none of the confidence intervals overlapped between the subgroup of men 40-59 years old and the subgroup of men 60-69 years old indicating that no common RR was compatible between these two population groups with any of these scenarios. So based on these analyses using a simplified modelling of the number of cases and of the rates, and the assumption that risk would be the same in both age groups, it can be concluded that the only value for RR that was somewhat compatible with the data was of the order of magnitude 1.31, after a 20-years induction period. All other lags and at-risk groups considered were not compatible with the data, when it was assumed that the risk would be the same in both age groups.

7.4 Estimation of power using the simplified statistical model

The power analyses were conducted on the subgroup of men aged 40-59 years old (Table 14, Table 15, Table 16). These numbers should be interpreted as follows: for the scenario in which all male 40-59 years old users of mobile phones had a postulated 20% increased RR of glioma (RR=1.2), 20 years after using their mobile phone for the first time (Table 14, row 6 of the lower panel, column 5), 76% of the simulated datasets correctly demonstrated a significantly increased estimated relative risk associated with the use of mobile phone, when the exposure distribution in the population was assumed to be that of the Nordic Interphone controls. So if this scenario was real, the simulated number of cases had 0.76 chance to demonstrate a statistically significantly increased RR, and a 0.24 chance of not demonstrating a statistically significant excess [in other words, if there existed other areas in the world that were exactly similar to the Nordic countries, in 76 out of 100 such areas we would correctly observe a statistically significantly increased RR]. A power of 100% was obtained when all the simulated datasets demonstrated a significantly increased estimated relative risk associated with the use of mobile phone for that scenario.

For men 40-59 years old, these exposure prevalences, combined dynamically with the induction periods of 0, 5, 10, 15, and 20 years led to a coherent picture: scenarios with shorter induction periods combined with higher simulated RR resulted in higher probabilities of detecting significant increases in the estimated RR, while scenarios with lower simulated RR, and longer induction periods had lower power. Low levels of hypothetical risk would not always lead to statistically significantly increased estimated risks, for all the exposure distributions that we considered, under the model assumptions. Simulations conducted with the exposure distribution of the Cosmos-France dataset had the lowest power. This is why the results of Table 16 are considered in the following.

Therefore, in these analyses of simulated datasets, we demonstrated that if the induction period was 10 years or more, risks lower than 1.1 for all users might not be detected, as the power was lower than 81% in some of the simulations. If the induction period was 15 years or more, risks lower than 1.2 might be undetected. If the induction period was 20 years or more, risks lower than 1.3 would be missed in approximatively 1 dataset in 5 or more.

When we hypothesized that the risk would only apply to those who qualified as high users of mobile phone, a similar picture emerged: if the risk applied only to those who had accumulated 339 lifetime hours of use, risks of 1.2 or lower might be missed in 1 dataset in seven, or more. If risk would be restricted to those who have accumulated 558 lifetime hours of use, risks of 1.2 or lower might be missed in 30 % or more of the datasets (power=70%). If risk would be restricted to those who have accumulated 896 lifetime hours of use, risks of 1.3 or lower might be missed in 17% or more of the datasets. If risk was restricted to those who have accumulated 1640 lifetime hours of use, risks of 1.4 or lower might be missed in 16% or more of the datasets. If risk was restricted to those who accumulated 1640 lifetime hours of use before the year 2003, risks of 2.0 might be missed in only 7% of the datasets (power = 93%), while if the risk was 1.5 or lower, it might be missed in 60% or more of the datasets (power = 40%) (Table 16).

7.5 Standardised Incidence Ratio analyses

In this set of analysis, we used statistical models accounting for other factors, together with the estimation of a possible mobile phone related risk. Standardised Incidence Ratios (SIR) analyses were carried out using these sophisticated statistical models (Methods paragraph 6.2.4, Table 17 to Table 32).

Specifically these analyses show that, among men 40-59 years old, assuming the prevalence of use was equal to that of the Nordic Interphone participants, when the group at-risk was all mobile phone users with a 5-years induction period, and when half of the baseline increase was modelled as unspecified, the ratio of the number of observed to the number of expected cases was 0.60 if the RR was assumed to be 2.5 (Table 17, row 1, cell 2). The sum of the observed cases was 60% (0.60) of the total of expected cases. The confidence interval (0.59-0.62) did not include 1, indicating that the expected number of cases, computed for this scenario, was statistically different from the observed number of cases and much higher. This scenario was rejected. The results of some of this set of analyses were illustrated in Figure 10, which shows the observed number of cases over time and the expected values for men aged 40-59 years old, based on the sophisticated SIR model, demonstrating when, over the period of observation, excesses and deficits of expected cases occurred compared to the observed numbers.

The main SIR analyses, which used the hypothesis that mobile phones might explain half of the increase in incidence rates, while other factors accounted for the other half of the increase, demonstrated that there was no scenario of risk that would be compatible between men 40-59 and men 60-69 years old (Table 17, Table 19, Table 21, Table 23, Table 25, Table 27, Table 29). Within each age subgroup, the results showed the same patterns for the 3 exposure distributions, namely from the Nordic Interphone, the Danish and the French Cosmos datasets. The SIR analyses carried out on men 40-59 years old showed that lower risks and longer induction periods appeared generally compatible with the data, irrespective of the exposure distribution considered. In the men 60-69 years old, scenarios of risk compatible with the observations were few; the majority of scenarios led to either a deficit or an excess of the expected number of cases, compared to the observed number of cases, and none were compatible with those of the age group 40-59 years old. In particular, analyses carried out on men 60-69 years old, showed that the scenarios with low risks and long

induction times led to a deficit of expected cases during the last years of observation, in contrast to those of the 40-59 years old men.

The analyses of scenarios in which risk was limited to heavy users led to a similar but more extreme picture (Table 18, Table 20, Table 22, Table 24, Table 26, Table 28). None of the scenarios that we considered were compatible with the data of both men aged 40-59 and men aged 60-69. Notably, there were hardly any scenarios that would fit the data of men aged 60-69 years old.

It had been decided a priori that a sensitivity analysis would be carried out, in which 75% of the baseline increase was modelled as unexplained factors, to gain insight into the data.

The picture was globally similar to the previous analysis but less extreme (Table 29 to Table 32). It led to few scenarios that were compatible with the data of both age groups. When the exposure distribution came from the Nordic Interphone dataset, the observed data was compatible with a scenario combining a risk of 1.08 and a 10 years induction period, and a scenario combining a risk of 1.3 and a 20 years induction period (Table 29, Table 31). When the exposure distribution was that of the Danish Cosmos participants, the observed data was compatible with a scenario combining a risk of 1.08 and a 10 years induction period (data not shown). No scenarios of risk were compatible between both age groups when the exposure distribution considered was that of the French Cosmos participants, but several scenarios were very close to compatibility (data not shown). Scenarios in which risk was limited to heavy users were also analyzed (Table 30, Table 32). None of the scenarios that we considered demonstrated compatibility between the data of men aged 40-59 and those of men aged 60-69. This was also true when the exposure distribution was modelled according to Cosmos-Denmark and Cosmos-France prevalences (data not shown). However, the SIR were more often closer to compatible than when half of the baseline was modelled.

8 Discussion

We analyzed the incidence rates of glioma in the Nordic countries, among the countries in the world with highest quality cancer diagnosis, health care mostly free of charge for the patient, and high quality cancer registration (ENGHOLM et al., 2010). Over the period of observation, glioma rates increased gradually. We detected no clear modification in the long-term time trends in the incidence rates of glioma in the Nordic countries during 2009-2016, overall or in any subgroup by country, age or gender, except for an overall decline since 2012 among Norwegian women, and a non-significant increase in the age group of Danish 20-39 years old men. Our results extend those of previous studies of time trends in the Nordic countries up to 2008 by adding 8 more calendar years of follow-up. These analyses are based on the entire adult population of Denmark, Finland, Norway and Sweden– a population base of 19.6 million people in the ages of 20 to 84 years in 2016 – and are strengthened by the comprehensive high-quality cancer registration in these countries.

The patterns were similar in men and women. Each country differed a little from the pattern observed in the pooled data showing that the dynamics were not exactly identical between the Nordic countries. The age group 20-39 demonstrated stable rates over the 38 years of observation and the age group 40-59 had non-significant changes during the same period. Statistically significant increases were observed in the age groups 60-69 and 70-84 years old. Among 60-69 years old in both sexes, the increases were regular over the whole observation period, and did not show signs that a plateau had been approached. Among 70-84 years old, in most of the countries, and in the combined dataset, marked increases in IR were observed over at least the last 12 years of observation, with the notable exception of those in the Finnish males. In Denmark and Norway, the rates ultimately

reached in this age group were higher than rates among 60-69 years old, possibly owing to more complete reporting procedures put in place in these countries since the early 2000.

In Norway, around 2000, the registry systematized the sending of out of reminders to hospitals when the administrative data (discharge or outpatient diagnosis) of the patient indicated a brain tumour (ICD-10 diagnosis of C70-72, D32–33 or D42–43), and no other sources (specifically histology report, clinical report, death certificate, or radiotherapy data), had data on the patient. In Denmark, in 1987, the reporting of cancers to the Danish Cancer Registry was changed from voluntary, with incentives, to compulsory. Between 2004 and 2008, the Danish Cancer Registry modified its reporting and registration process, which, among others, introduced electronic notification of the cases, and sending out of reminders based on information on cancers in the Danish National Patient Registry, the Danish Pathology Register, or the Danish Register of Causes of Death, when the cancer was not known to the Danish Cancer Registry (GJERSTORFF, 2011). In Sweden, in contrast, the careful comparison of various sources of data over the period 1990-2014 revealed a large underestimation of the number of cases in the cancer registry, that was stable over time at around 10% for malignant brain tumours (TETTAMANTI et al., 2019).

Over the study period, access to very specific imaging techniques became a necessary element of routine care in high income countries (FONTANA, BENZINGER, COBBS, HENSON, & FOUKE, 2014; FOUKE et al., 2015; LUNDY et al., 2020; OVERCAST et al., 2021). However, in Denmark, the first ever CT-scan was installed in 1974, in the capital city, and the second in 1976, outside the capital city. MRI technology was developed and deployed later: the first ever MRI machine was put in use in 1984, the next 3 MRIs became available in 1989 in that country (Christoffer Johansen, personal communication). Similar level of equipment is likely to have happened around the same time in the other Nordic countries. At the end of our study period, treatment guidelines established by the European Association for Neuro-Oncology recommend that „a decision for palliative care without histological diagnosis should be avoided unless the risk of the biopsy procedure is considered too high or if the prognosis is likely to be very unfavourable, e.g., in old patients with large tumors and rapid clinical decline“ (WELLER et al., 2017). General state of health in the population in their sixties and of the ages 70-84 has improved over the past decades, as evidenced by increases in life expectancy, which is also likely to have contributed to an increased number of surgeries and biopsies being carried out. An additional potential explanation of the observed increases in the older age groups might be a reduced likelihood of competing causes of death, if diagnostic interval and patient interval became shorter over the many decades between 1979 and 2016; we have no data to support this hypothesis, however.

In addition, at least since the early 2000, it has been recognised that the loss of heterozigosity (LOH) with codelition of 1p/19q is a factor of better prognosis for oligodendroglioma patients, since it marks an improved response to chemotherapy (ENGELHARD, 2002). This, together with the later discovery of other molecular markers has very likely contributed to increased rates of surgeries and of biopsies, and refined pathological diagnosis, especially among patients previously considered inoperable. The combination of these factors is likely to have played an important role in the diagnosis and reporting of cases, especially older cases to the registry. A fraction of the tumours previously deemed inoperable might have been operated, increasing the likelihood of reporting to the registries.

When examining the trends by subtypes, glioblastoma generally increased while other high grade gliomas decreased, and low grade glioma were stable in the most recent period, except in Denmark where low grade glioma rates increased among men and women in the last 3 years of observation. In Sweden, the rates of glioblastoma underwent most changes, namely the increase in glioblastoma

rates in Sweden in the years after the introduction of that code by the cancer registry, since a new code is not mandatorily fully used immediately after it is introduced.

Use levels were obtained from 3 different populations covering a range of exposure situations. We considered possible lags, from 0 to 20 years and different at-risk groups among users based on prior studies which resulted in a range of sizes of potentially at-risk populations. While interviews of the controls for the Interphone study were conducted in the years 2000-2003 in these countries in a random sample of the general population, data from Cosmos-Denmark study was sampled among mobile phone users in 2007-2009. Only one attempt has been made to validate the recall of the start of mobile phone use. This was conducted on data collected in 2007, and found that there was on average, a declaration 0.71 years (8.4 months) earlier by controls than what the operators had registered, with large variability (SD = 4.17 years) (PETTERSSON et al., 2015). Data suggested a tendency for positive errors (operators start date earlier than self-report) when reporting late start years and negative errors (operators start date later than self-report) when early start years were reported. Due to the design of the recruitment of the studies, information on the age group 60-69 years old was limited to the later years of each study, while for earlier years, rates were extrapolated from the patterns in the other age groups.

If the occurrence of glioma were associated to the use of mobile phones, the change in prevalence of use from zero to nearly 100% over a 20-30-years period would eventually influence the time trends of the incidence rates of these tumours. Conversely, an absence of change in the time trends, at any point in time, would constitute evidence against this association. To evaluate this question, we examined with various statistical methods the observed number of cases of glioma and the glioma rates among 40-59 years old males and 60-69 years old males, which were the gender and age groups who had highest use of mobile phone in the past. There has been no evidence so far of different mobile phone related risks between these age groups, and therefore we expected the risk, if any, to be the same in these 2 age groups.

When Poisson regressions were adjusted to the observed number of cases, conditional to the exposure prevalence, the observed excess RR were mostly not coherent between the two age groups. Confidence intervals did not overlap, except when the longest latency of 20 years was considered. The scope of these analyses was limited by the simplifying modelling assumption that the baseline incidence rate would be constant, a questionable model, especially for the older population considered.

Further sophisticated statistical analyses relaxing this assumption provided similar results. In particular, in our main SIR analysis, we did not find scenarios of risk in which the observed data of both the 40-59 years and those of the 60-69 years old men were compatible with their expected values under the scenario considered. This appears to indicate that our risk scenarios, covering a wide range of mobile phone related risks, together with the assumptions on the incidence rate increases and the exposure distribution were not mimicking the reality.

When, in our sensitivity SIR analysis, we assumed that 75% of the baseline incidence rate increase was explained by other factors, a very limited number of scenarios appeared compatible between both age groups, if the exposure distribution was that observed among the Nordic Interphone controls, or the Danish Cosmos study, but not the French Cosmos dataset. The scenario that was compatible with the observed data involved a small risk increase for all users of mobile phones (RR = 1.08) with an induction period of 10 years. A risk of 1.3 after an induction period of 20 years also appeared compatible with the observed number of cases when the exposure distribution was that of the Nordic Interphone controls, but not the other exposure distributions considered.

To sum up, our simplified and more sophisticated analyses appeared to indicate that the small increase in IR of men age 40-59 and the marked increase in RR of men aged 60-69 were generally not compatible with the same mobile phone related risks increases. When models in which the totality of the IR increases were assumed to be associated with mobile phone effects, a RR of 1.31 that would start 20 years after first using a mobile phone was borderline compatible between these 2 age groups, while all other induction periods (0, 5, 10, 15 years) or heavy users risk scenarios produced RR estimates and CI which did not overlap between the 2 age groups when the same exposure distribution was considered. When half of the IR increases were attributed to other factors, none of the mobile phone related risks scenarios were compatible with the data, in the SIR analyses (assuming the same risk in both age groups). When most (75%) of the IR increases were attributed to other factors, then small excess risks (RR= 1.08 applying to all users after 10 years) or risks after long latencies (RR = 1.3 applying to all users after 20 years) were compatible with the observed incidence rates and exposure distributions that we assumed. Further work on these scenarios could shed more light on the remaining uncertainties. Of note, scenarios of risks limited to heavy users groups did not appear compatible with the observed number of cases in these analyses.

Several case-control and cohort studies have evaluated the association between mobile phone use and glioma risk. The results of our simulation study were compatible with studies showing no increased risks of gliomas (BENSON et al., 2013; FREI et al., 2011);

The association between mobile phone use and malignant brain tumours has also been evaluated in several Swedish case-control studies, and a pooled analysis of most of these results has been published (HARDELL et al, 2015). The pooled study, with case ascertainment periods between 1997 and 2000, between 2000 and 2003 and between 2007 and 2009, yielded markedly elevated risks: OR for any type of phone use after 1 year induction period of 1.3 (95%CI 1.1–1.6), OR for phone use longer than 10 years of 1.4 (95%CI 1.1–1.9) or higher (Table 1, label 1 and 2) (HARDELL & CARLBERG, 2015). We found that these highly increased risks were in strong contradiction with the incidence time trends in the Nordic countries up to 2016, a conclusion drawn from the simplified and the sophisticated statistical modellings of scenarios of risk in both age groups. Although the definition of cases is slightly different, we reiterate our previous conclusion, that the presence of biases and errors in the self-reported mobile phone use may have resulted in the unrealistically high Odds-Ratios found in these studies (Table 1, label 1 and 2). The CERENAT study reported an increased risk, of 1.78 (95%CI = 0.98 to 3.24) for 339 hours of mobile phone use or more (Table 1, label 3). Neither the simplified, nor the sophisticated statistical modelling of this scenario of risk appeared compatible with a RR of this magnitude. The same study also reported a risk of 2.89 (95% CI 1.41 to 5.93) for people who would have had more than 896 hours of mobile phone use (Table 1, label 4). We found that this highly increased risk was not compatible with the data of the 40-59 year old men in our analyses, but the sophisticated statistical models showed that these risks could be compatible with the increases observed in 60-69 years old men, under the assumption that half of the baseline increase was related to mobile phone risk. No study has so far reported that mobile phone related risk would be markedly different between age groups, with increased risks limited to the age group of people above 60, and no increased risks in younger ages; so we believe that these results were therefore demonstrating rather an absence of risk in both age group, but it deserves follow-up in further studies. Analyses in which this level of use would have led to a risk if it were related to GSM use only were not compatible with the observations (Table 1, label 4).

A separate analysis of the Canadian dataset of the Interphone study has been published (Table 1, label 5). In our analyses, risks of these magnitude were not compatible with the observed number of cases in the age group 40-59, which were included in this study. They were, however, compatible with the observed number of cases in some of the analyses of the age group 60-69 years old, an age

group not included in this study. In the analysis of the international Interphone study, an elevated risk (OR = 1.4, 95%CI 1.0-1.9) among the 10% heaviest users was also reported, although bias was discussed as an alternative explanation for this finding (Table 1, label 6). Our main SIR models applied to data of men 40-59 years old showed that this scenario of risk was not compatible with the data when the exposure distributions were those of the Nordic Interphone controls or the Cosmos-Denmark participants, while this scenario of risk was compatible with the observed data if we assumed that the exposure distribution was that of the French Cosmos study. If we assumed that only those who had reached that level of use before 2003 were at risk, as a proxy for GSM exposure, in the age group 40-59 years old, the observed number of cases were compatible with the expected number of cases for the Cosmos-Denmark and the Cosmos-France exposure distribution (Table 1, label 6).

Our simulation study is not free of assumptions. The induction period relating mobile phone use and glioma risk, if such an association exists, is unknown, so is the magnitude of the risk, and the real patterns may be more complex than the scenarios that we simulated. In addition, there are several factors that we did not account for. The coverage of the Nordic cancer registries was not complete, but some 1.5% to 10% of the malignant tumours were missed in this age group. In Sweden, it has been estimated that completeness would not have changed over the period 1998-2014, while completeness might have improved in other countries. We modelled that other, yet to be discovered, risk factors of the disease as well as improvement in its detection and reporting had a smooth, gradual impact, over the period 1979–2016, which is consistent with the gradually increasing IR. We used 3 sources of information on the use of mobile phones, all self-reported, to evaluate the prevalence of use and heavy use up to 2002, 2008 or 2016 and extrapolated the prevalences for the periods and age groups for which no data was available, based on the trends observed in the other age groups. The use of hands-free devices was not accounted for, although this was not frequent in these populations (data not shown).

In conclusion, it is difficult to demonstrate the absence of risk, in real life condition, and assumptions about the impact of the improvement of diagnosis tools, treatment and registration changes over time were used in our simulations. However, based both on the observed IR and the simulations, we reiterate and strengthen our previous conclusion that, the risk, should one exist, ought to be lower or occur after a longer induction period or act on a smaller population, or a combination of these, than most of the level of risk that have been reported in previously published case-control studies.

9 Conclusions

In this project we projected incidence rates of glioma under various scenarios of mobile phone-associated increased glioma risks, and compared them with the observed incidence rates in the Nordic countries. The comparison was carried out on the data of men aged 40 to 69 years. The modelled scenarios included risk increases reported from analytical epidemiological studies, which were all of case-control design. Most of those results were shown to be implausible in our simulations, implying that biases and errors in the self-reported use of mobile phones have likely distorted their findings. An increased risk in the 10% heaviest mobile phone users was an exception to this general situation, as it remained plausible. Results of cohort studies showing no association were compatible with observed incidence rates. We also studied what hypothetical mobile phone-related risks were conceivable if the changes in incidence rates in 40-59 year old and 60-69 year old men were fully attributable to mobile phone use. The fact that we observed different hypothetical risks in these two age groups while research at present has not suggested that older men should have higher risk related to mobile phone use than younger men, does not align with the assumption

that mobile phone exposures caused the incidence rate trends. This ecological data is not sufficient to dismiss every potential mobile phone related risk scenario, but suggests that the risk – if it exists - would be very small, only occur after very long latency periods of several decades, or only affect small subgroups within glioma patients.

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11 Tables and figures

Table 1: Selected elevated risks of glioma or of malignant brain tumours reported in the scientific literature.

Identification of reference	Period of case recruitment	Size of case-control study	Exposure definition	OR	95% CI	Label of analysis for reference
Hardell and Carlberg (2015)	1997-1999, 2000-2003, and 2007-2009	1498 malignant brain tumours cases; risk analysis on 1380 glioma cases and 3430 controls	use of mobile phones more than one year	1.3	1.1 to 1.6	1
Hardell and Carlberg (2015)	1997-1999, 2000-2003, and 2007-2009	1498 malignant brain tumours cases; risk analysis on 1380 glioma cases and 3430 controls	10 to 15 years after first using a mobile phone (higher risks reported for persons exposed longer)	1.4	1.1 to 1.9	2
Cerenat (2014)	2004–2006	253 gliomas cases and 892 matched controls	self-reported lifetime cumulative mobile phone conversations ≥ 339 hours	1.78	0.98 to 3.24	3
Cerenat (2014)	2004–2006	253 gliomas cases and 892 matched controls	self-reported lifetime cumulative mobile phone conversations ≥896 hours	2.89	1.41 to 5.93	4
Interphone (Canada) (2017)	2001-2004	170 gliomas cases and 653 controls	>558 hours of cumulative hours of use	2.0	1.2 to 3.4	5
Interphone international study (13 countries) (2010)	2000-2004	2708 gliomas cases and 2972 matched controls	self-reported lifetime cumulative mobile phone conversations ≥1640 hours	1.40	1.03 to 1.89	6

Notes: OR: Odds-ratio; CI: confidence interval.

Table 2: Average incidence rate (IR) of gliomas between 2007 and 2016, number of incident cases (N) in 2016 and population at risk in millions (Pop) in 2016 by country, tumour type among men.

	Nordic countries (Pop=9.8)				Denmark (Pop = 2.1)				Finland (Pop = 2.1)				Norway (Pop = 1.9)				Sweden (Pop =3.7)			
Tumour type	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**
All gliomas[a]*	*1033*	9.1	8.4	9.6	*263*	9.7	8.1	11.0	*185*	8.0	7.0	8.5	*205*	10.3	9.5	10.8	*380*	8.8	8.1	9.4
Glioblastomas	*689*	5.7	5.0	6.0	*179*	6.8	5.6	7.8	*114*	4.4	3.8	4.7	*130*	6.2	5.5	7.1	*266*	5.5	4.7	6.1
Other High Grade Gliomas	*167*	1.7	1.6	2.1	*43*	1.8	1.6	2.4	*34*	1.8	1.4	2.2	*40*	2.1	1.9	2.3	*50*	1.5	1.3	1.9
Low Grade Gliomas	*166*	1.6	1.4	1.8	*34*	1.0	0.3	1.7	*34*	1.8	1.6	2.0	*35*	1.9	1.3	2.6	*63*	1.7	1.5	2.0

*Notes: AIR : average incidence rate, LIR: lowest incidence rate, HIR : highest incidence rate. [a]: gliomas, excluding medulloblastomas and glial neuronal tumours; *: gliomas whose grades were not assigned (total N=65) not presented separately, includes in Denmark N=31, in Finland N= 10, in Norway N=7, in Sweden N=17.*

Table 3: Average incidence rate (IR) of gliomas between 2007 and 2016, number of incident cases (N) in 2016 and population at risk in millions (Pop) in 2016 by country, tumour type among women.

	Nordic countries (Pop=9.8)				Denmark (Pop = 2.2)				Finland (Pop = 2.1)				Norway (Pop = 1.9)				Sweden (Pop =3.7)			
Tumour type	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**	**N**	**AIR**	**LIR**	**HIR**
All gliomas[a]*	*691*	6.1	5.9	6.3	*183*	6.5	5.8	7.3	*135*	5.6	5.1	6.2	*113*	6.8	5.3	7.9	*260*	5.9	5.4	6.5
Glioblastomas	*455*	3.5	3.1	3.8	*118*	4.1	3.4	4.8	*85*	2.7	2.3	3.1	*71*	4.0	3.2	4.8	*181*	3.3	2.9	4.1
Other High Grade Gliomas	*124*	1.3	1.1	1.6	*35*	1.5	1.1	1.9	*21*	1.3	0.9	1.6	*31*	1.4	1.0	1.7	*37*	1.1	0.8	1.3
Low Grade Gliomas	*107*	1.3	1.1	1.5	*29*	0.8	0.4	1.4	*28*	1.5	1.4	2.3	*10*	1.4	0.5	2.4	*40*	1.4	1.1	1.8

*Notes: AIR : average incidence rate, LIR: lowest incidence rate, HIR : highest incidence rate. [a]: gliomas, excluding medulloblastomas and glial neuronal tumours; *: gliomas whose grades were not assigned (total N=71) not presented separately, includes in Denmark N=25, in Finland N= 14, in Norway N=17, in Sweden N=15.*

Table 4: Annual Percent Change in glioma incidence rates among men aged 20-84 years old in the Nordic countries combined and in Denmark, Finland, Norway and Sweden, estimated with the best fitting joinpoint model, for the period 1979-2016.

Countries	Segments	Beginning of segment	End of segment	APC	LCI	UCI
Nordic countries combined	-	1979	2016	0.6	0.4	0.7
Denmark	-	1979	2016	0.5	0.2	0.8
Finland	-	1979	2016	0.9	0.7	1.1
Norway	1	1979	1995	0	-1.1	1.2
	2	1995	1999	8.7	-4.2	23.3
	3	1999	2016	-0.1	-0.9	0.6
Sweden	1	1979	1984	5.9	0.9	11.0
	2	1984	2001	-0.9	-1.6	-0.1
	3	2001	2016	1.1	0.3	1.9

Notes. APC: Annual Percent Change; CI: Confidence Interval; LCI: lower bound of 95% confidence interval; UCI: upper bound of 95% confidence interval.

Table 5: Annual Percent Change in glioma incidence rates among women aged 20-84 years old in the Nordic countries combined and in Denmark, Finland, Norway and Sweden, estimated with the best fitting joinpoint model, for the period 1979-2016.

Countries	Segments	Beginning of segment	End of segment	APC	LCI	UCI
Nordic countries combined	-	1979	2016	0.3	0.2	0.5
Denmark	-	1979	2016	0.4	0.1	0.6
Finland	-	1979	2016	0.5	0.2	0.8
Norway	1	1979	2012	1.3	0.8	1.8
	2	2012	2016	-6.4	-15.6	3.8
Sweden	-	1979	2016	0	-0.3	0.2

Notes. APC: Annual Percent Change; CI: Confidence Interval; LCI: lower bound of 95% confidence interval; UCI: upper bound of 95% confidence interval.

Table 6: Annual Percent Change in glioma incidence rates among men by age groups in the Nordic countries combined and in Denmark, Finland, Norway and Sweden, estimated with the best fitting joinpoint model, for the period 1979-2016.

	20-39 years					40-59 years					60-69 years					70-84 years				
Countries	**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**	
Nordic countries combined	-	1979	2016	0.2	-0.1	0.5	-	1979	2016	0.1	0	0.3	-	1979	2016	0.6	0.4	0.9	1	1979	1984	7.3	-0.4	15.6
																			2	1984	1990	-4.5	-11	1.9
																			3	1990	2016	3.1	2.6	3.5
Denmark	1	1979	1987	3.9	-1.2	9.2	-	1979	2016	0	-0.3	0.3	-	1979	2016	0.5	0.1	1.0	1	1979	1993	-2.5	-5.4	0.5
	2	1987	2013	-2.0	-3	-1.0													2	1993	2016	5.1	4	6.3
	3	2013	2016	21.1	-5.8	55.8																		
Finland	-	1979	2016	0.3	-0.2	0.9	-	1979	2016	0.6	0.2	1.0	-	1979	2016	0.9	0.4	1.4	1	1979	1999	4.6	2.2	7.1
																			2	1999	2016	0.3	-1.4	2.2
Norway	-	1979	2016	0.6	0	1.2	-	1979	2016	0.4	-0.2	0.9		1979	2016	1.4	0.9	1.9	1	1979	1994	-0.3	-4.1	3.7
																			2	1994	1997	30.5	-33	152.6
																			3	1997	2016	1.8	0.3	3.3
Sweden	1	1979	1985	9.0	0.7	18.1	1	1979	1984	7.9	2.3	13.8	-	1979	2016	0.4	0	0.7	1	1979	2004	-1	-2	0.1
	2	1985	2016	-0.4	-1	0.2	2	1984	1991	-3.3	-6.7	0.4							2	2004	2016	5.4	2.8	8.1
							3	1991	2016	0.1	-0.3	0.5												

Notes: S: Segment; APC: Annual Percent Change; CI: Confidence Interval.

Table 7: Annual Percent Change in glioma incidence rates among women by age groups in the Nordic countries combined and in Denmark, Finland, Norway and Sweden, estimated with the best fitting joinpoint model, for the period 1979-2016.

	20-39 years					40-59 years					60-69 years					70-84 years				
Countries	**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**	
Nordic countries combined	-	1979	2016	0.2	-0.1	0.5	-	1979	2016	-0.2	-0.3	0.0	-	1979	2016	0.4	0.2	0.7	1	1979	1994	0.2	-1.0	1.3
																			2	1994	2016	2.8	2.3	3.3
Denmark	-	1979	2016	0.3	-0.3	0.9	-	1979	2016	-0.4	-0.8	0.0	-	1979	2016	0.5	0.0	1.0	1	1979	1994	-2	-4.1	0.3
																			2	1994	2016	4.2	3.1	5.2
Finland	-	1979	2016	-0.1	-0.7	0.5	-	1979	2016	-0.1	-0.5	0.4	-	1979	2016	0.9	0.2	1.5	-	1979	2016	2.7	2.0	3.3
Norway	-	1979	2016	0.7	-0.1	1.5	-	1979	2016	0.0	-0.6	0.6	-	1979	2016	1.2	0.7	1.8	1	1979	2008	5.2	4.1	6.3
																			2	2008	2016	-1.6	-6.2	3.2
Sweden	-	1979	2016	0.0	-0.6	0.5	-	1979	2016	-0.1	-0.5	0.2	-	1979	2016	-0.2	-0.6	0.2	1	1979	2003	-1.2	-2.0	-0.3
																			2	2003	2016	4.2	2.1	6.3

Notes: S: Segment; APC: Annual Percent Change; CI: Confidence Interval.

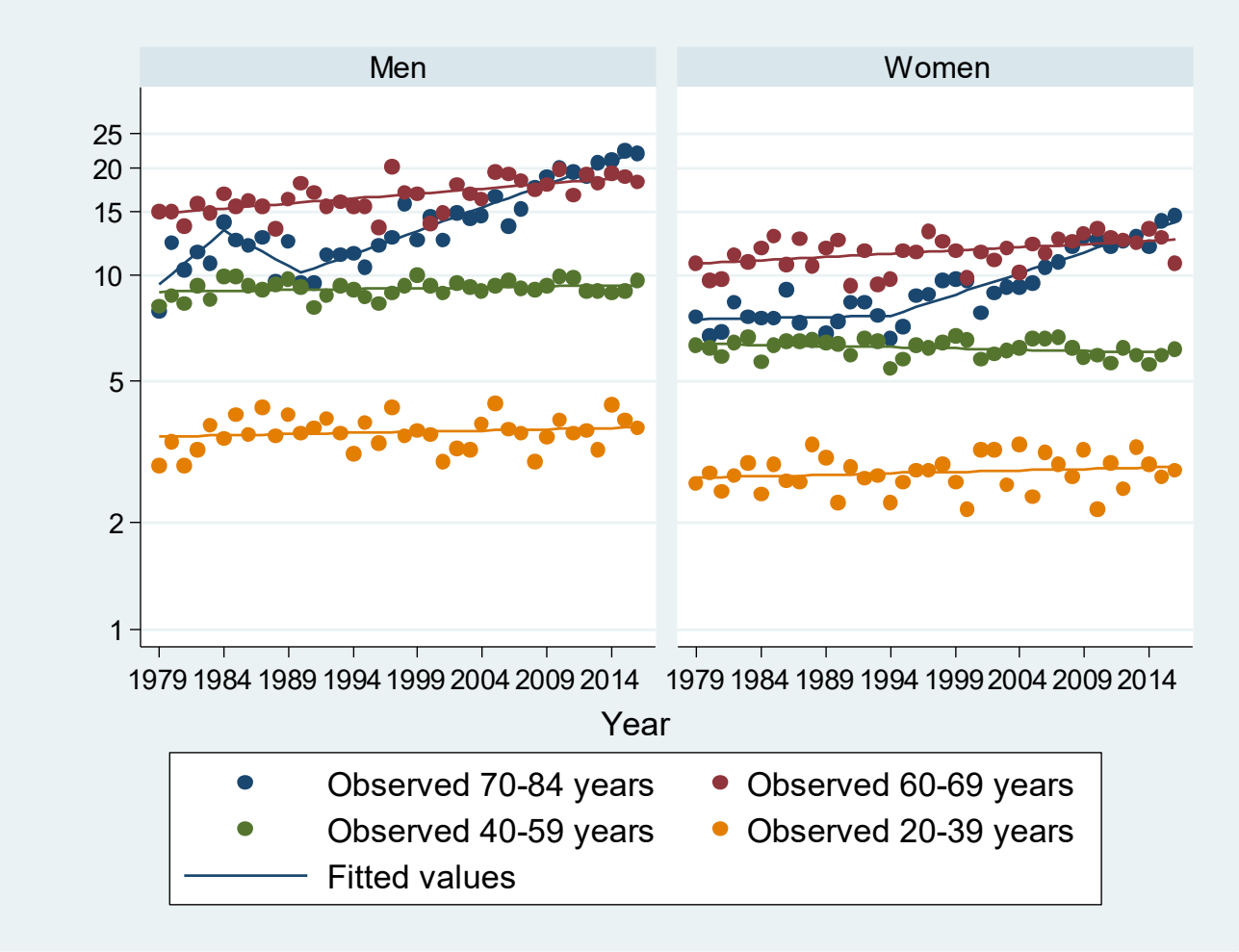

Figure 1: Glioma incidence rates in the Nordic countries (Denmark, Finland, Norway and Sweden), 1979 to 2016, observed and fitted with the best-fitting joinpoint model among 20 to 39 (gold), 40 to 59 (green), 60 to 69 (dark red) and 70-84 years old (dark blue) men and women, on a logarithmic scale.

Table 8: Annual percent change in glioblastoma, other high grade gliomas and low grade gliomas incidence rates among men aged 20-84 years old in the Nordic countries combined and in each country, estimated with the best fitting joinpoint model, for the period 1990-2016.

	Glioblastomas						Other high grade gliomas						Low grade gliomas					
Countries	**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**	
Nordic countries combined	1	1990	1998	9.4	7.2	11.7	1	1990	1995	-5.8	-9.8	-1.6	1	1990	1996	-7.6	-12	-2.5
	2	1998	2001	-3.8	-17.5	12.2	2	1995	2016	-1.4	-1.9	-0.9	2	1996	2016	0.3	-0.6	1.3
	3	2001	2016	2.4	1.9	3.0												
Denmark	-	1990	2016	2.0	1.4	2.6	1	1990	2005	6.5	4.1	9.0	1	1990	2013	-5.8	-7.1	-4.6
							2	2005	2016	-3.2	-6	-0.4	2	2013	2016	32.6	-1.7	79.0
Finland	1	1990	1994	11.6	2.4	21.7	-	1990	2016	1.8	0.9	2.7	-	1990	2016	0.7	-0.5	1.8
	2	1994	2006	-1	-2.4	0.5												
	3	2006	2016	1.9	0.4	3.5												
Norway	-	1990	2016	1.2	0.5	1.9	1	1990	2000	14.5	8.7	20.6	-	1990	2016	0.3	-0.7	1.3
							2	2000	2016	-0.1	-1.7	1.4						
Sweden	1	1990	1993	NA	-	-	1	1990	1996	-10.2	-13.5	-6.8	1	1990	1996	-11.2	-17	-5.5
	2	1993	2016	3.8	3	4.5	2	1996	2004	-2.9	-6.4	0.8	2	1996	2016	1.4	0.3	2.6
							3	2004	2007	-17.2	-41.4	17.2						
							4	2007	2016	-0.5	-3.9	3.0						

Notes: S: Segment; APC: Annual Percent Change; CI Confidence Interval. All tumours were located in the brain (ICD-O 3 topographic code C71). Gliomas were defined as all tumours registered under the ICDO-3 morphological codes 9380 to 9460, with the exclusion of the codes 9412 and 9413. Among these, glioblastomas were the tumours registered under the ICDO-3 morphological codes 9440/3, 9441/3, 9442/3, other high grade gliomas were the tumours registered under the ICDO-3 morphological codes 9380/3, 9381/3, 9382/3, 9390/3, 9392/3,

9401/3, 9451/3, 9460/3 and low grade gliomas were the tumours registered under the ICDO-3 morphological codes 9383/1, 9384/1, 9391/3, 9393/3, 9394/1, 9394/3, 9400/3, 9410/3, 9411/3, 9420/3, 9421/1, 9421/3, 9424/3, 9444/1, 9450/3.

Table 9: Annual percent change in glioblastomas, other high grade gliomas and low grade gliomas incidence rates among women aged 20-84 years old in the Nordic countries combined and in each country, estimated with the best fitting joinpoint model, for the period 1990-2016.

	Glioblastomas						Other high grade gliomas						Low grade gliomas					
Countries	**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**		**S**	**period**		**APC**	**95% CI**	
Nordic countries combined	1	1990	1997	7.5	4.6	10.5	-	1990	2016	-2.0	-2.4	-1.6	1	1990	1995	-6.4	-13	0.8
	2	1997	2016	1.6	1.1	2.0							2	1995	2016	0.4	-0.5	1.3
Denmark	-	1990	2016	1.7	1.1	2.3	1	1990	2007	4.9	2.9	6.9	1	1990	2013	-4.9	-6.4	-3.3
							2	2007	2016	-2.8	-6.5	1.1	2	2013	2016	25.8	-12	79.0
Finland	-	1990	2016	0.3	-0.4	1.1	1	1990	1993	-18.3	-35.3	3.2	-	1990	2016	0.8	-0.4	2.0
							2	1993	2005	6.1	2.6	9.7						
							3	2005	2016	-2.9	-5.8	0.0						
Norway	1	1990	2012	2.1	1.4	2.8	1	1990	1998	22.4	9.6	36.8	-	1990	2016	-0.1	-1.7	1.6
	2	2012	2016	-6.3	-13.9	1.9	2	1998	2016	-0.8	-2.6	1.1						
Sweden	1	1990	1993	NA	-	-	1	1990	2010	-7.0	-7.8	-6.1	1	1990	1995	-12.2	-20	-3.5
	2	1993	2016	3.2	2.4	4.0	2	2010	2016	1.1	-6.5	9.3	2	1995	2012	3.4	1.7	5.1
													3	2012	2016	-8.4	-19	3.8

Notes: S: Segment; APC: Annual Percent Change; CI Confidence Interval. All tumours were located in the brain (ICD-O 3 topographic code C71). Gliomas were defined as all tumours registered under the ICDO-3 morphological codes 9380 to 9460, with the exclusion of the codes 9412 and 9413. Among these, glioblastomas were the tumours registered under the ICDO-3 morphological codes 9440/3, 9441/3, 9442/3, other high grade gliomas were the tumours registered under the ICDO-3 morphological codes 9380/3, 9381/3, 9382/3, 9390/3, 9392/3, 9401/3, 9451/3, 9460/3 and low grade gliomas were the tumours registered under the ICDO-3 morphological codes 9383/1, 9384/1, 9391/3, 9393/3, 9394/1, 9394/3, 9400/3, 9410/3, 9411/3, 9420/3, 9421/1, 9421/3, 9424/3, 9444/1, 9450/3.

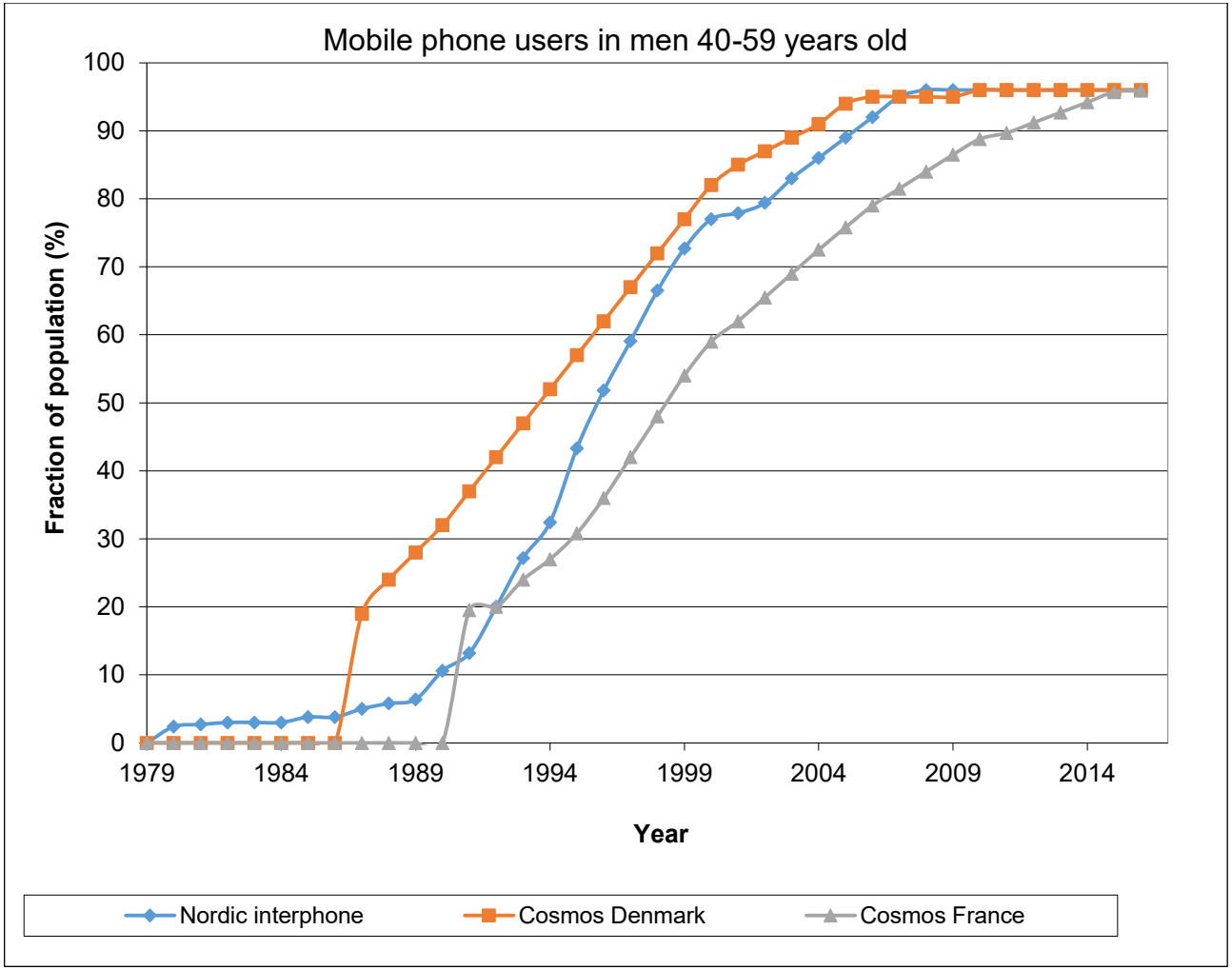

Figure 2:Self-reported prevalence of mobile phone use among men aged 40-59 years old interviewed in the Nordic countries as Interphone study's controls in 2001-2003, interviewed for the Cosmos study in Denmark in 2007-2009, and interviewed for the Cosmos study in France in 2019.

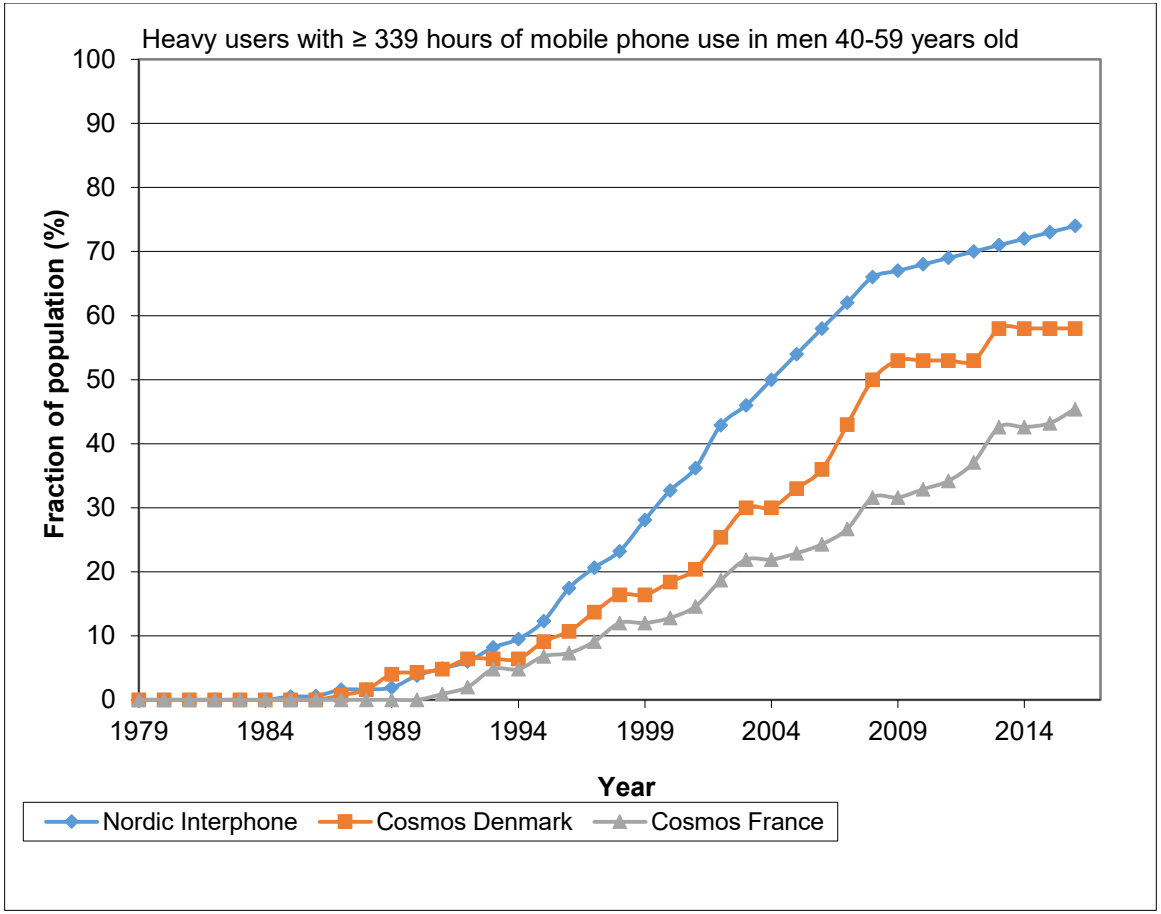

Figure 3: Self-reported prevalence of heavy use, defined as accumulated lifetime conversation time of more than 339 hours of use among men aged 40-59 years old interviewed in the Nordic countries as Interphone study's controls in 2001-2003, interviewed for the Cosmos study in Denmark in 2007-2009, and interviewed for the Cosmos study in France in 2019.

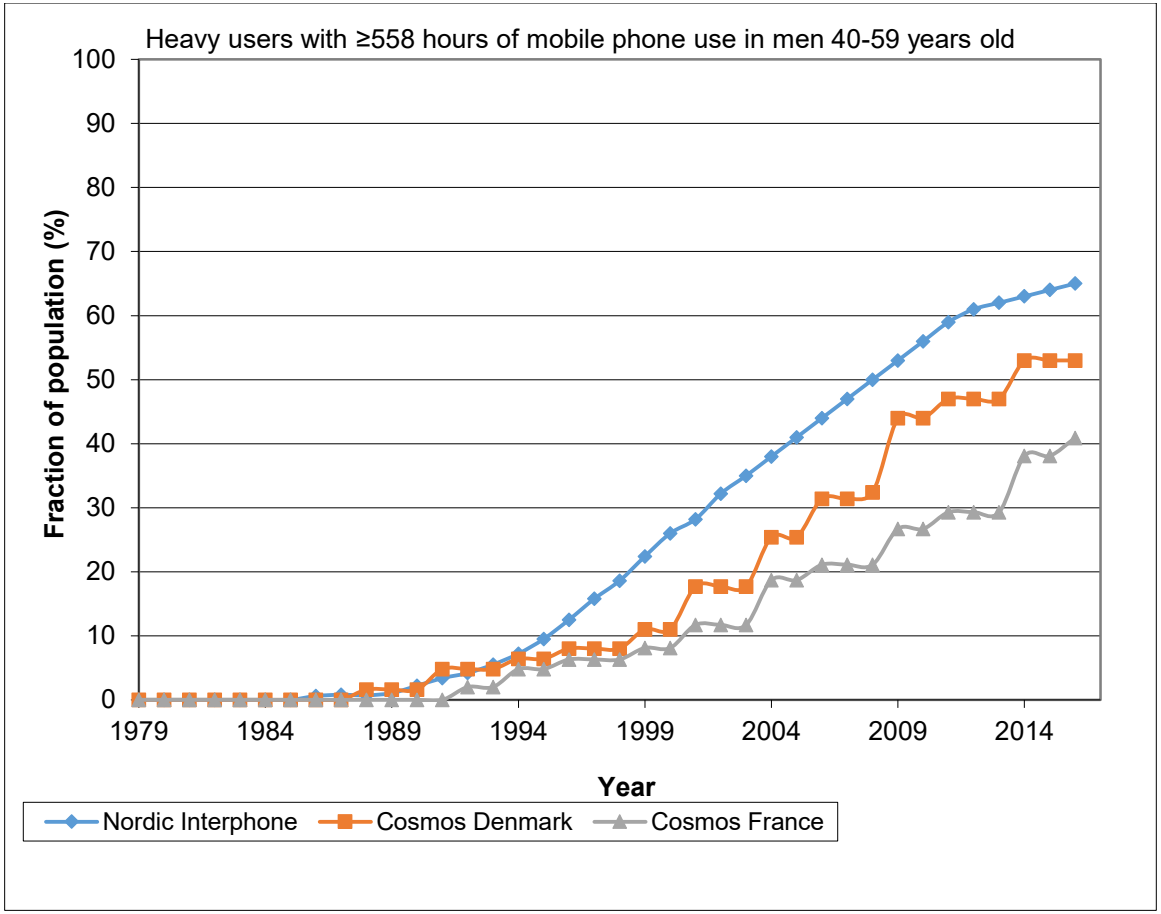

Figure 4: Self-reported prevalence of heavy use, defined as accumulated lifetime conversation time of more than 558 hours of use among men aged 40-59 years old interviewed in the Nordic countries as Interphone study's controls in 2001-2003, interviewed for the Cosmos study in Denmark in 2007-2009, and interviewed for the Cosmos study in France in 2019.

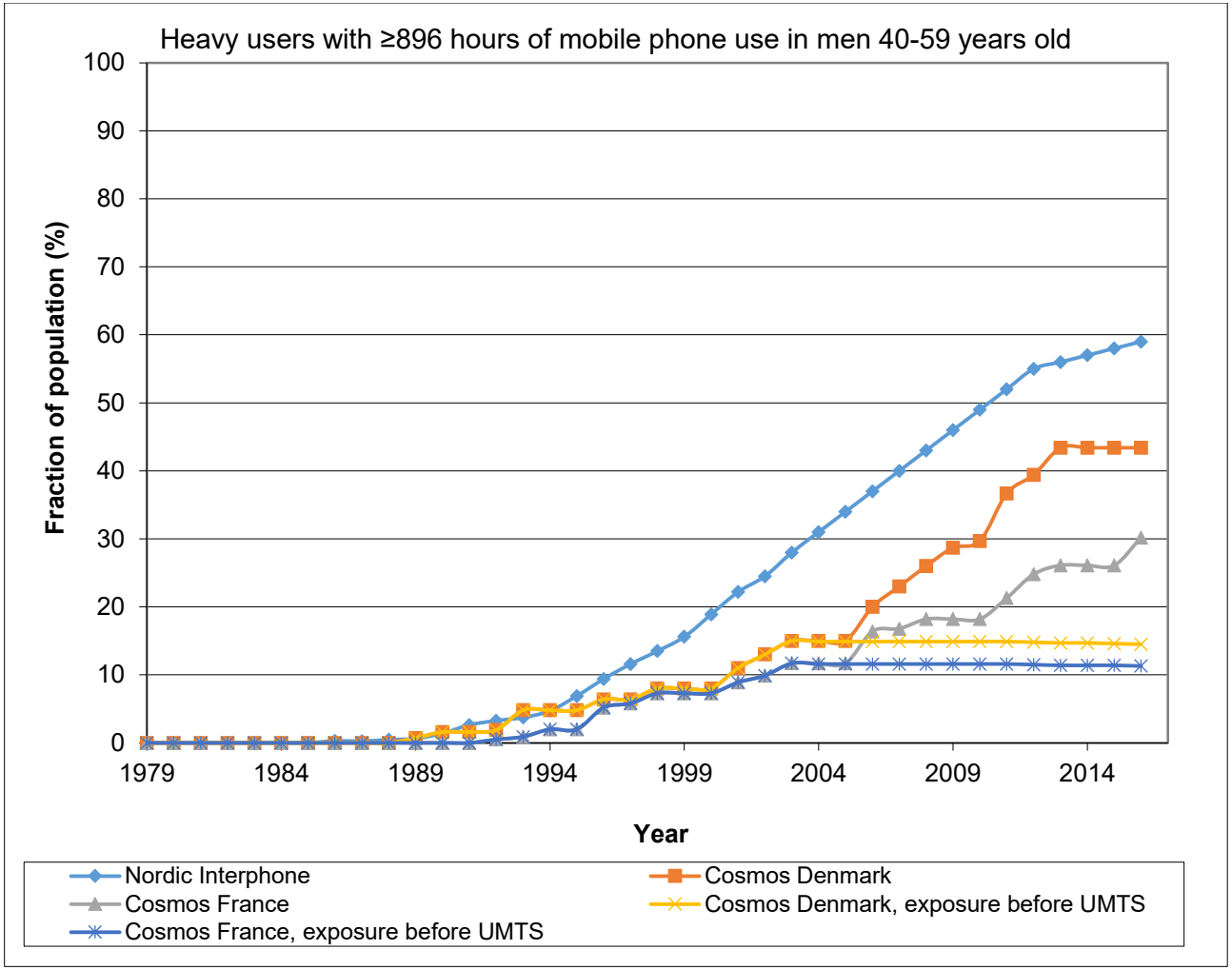

Figure 5: Self-reported prevalence of heavy use, defined as accumulated lifetime conversation time of more than 896 hours of use among men aged 40-59 years old interviewed in the Nordic countries as Interphone study's controls in 2001-2003, interviewed for the Cosmos study in France in 2019. The exposure situation characterised by 896 hours of use accumulated before 2003 (approximating GSM but not UMTS /LTE) is also presented.

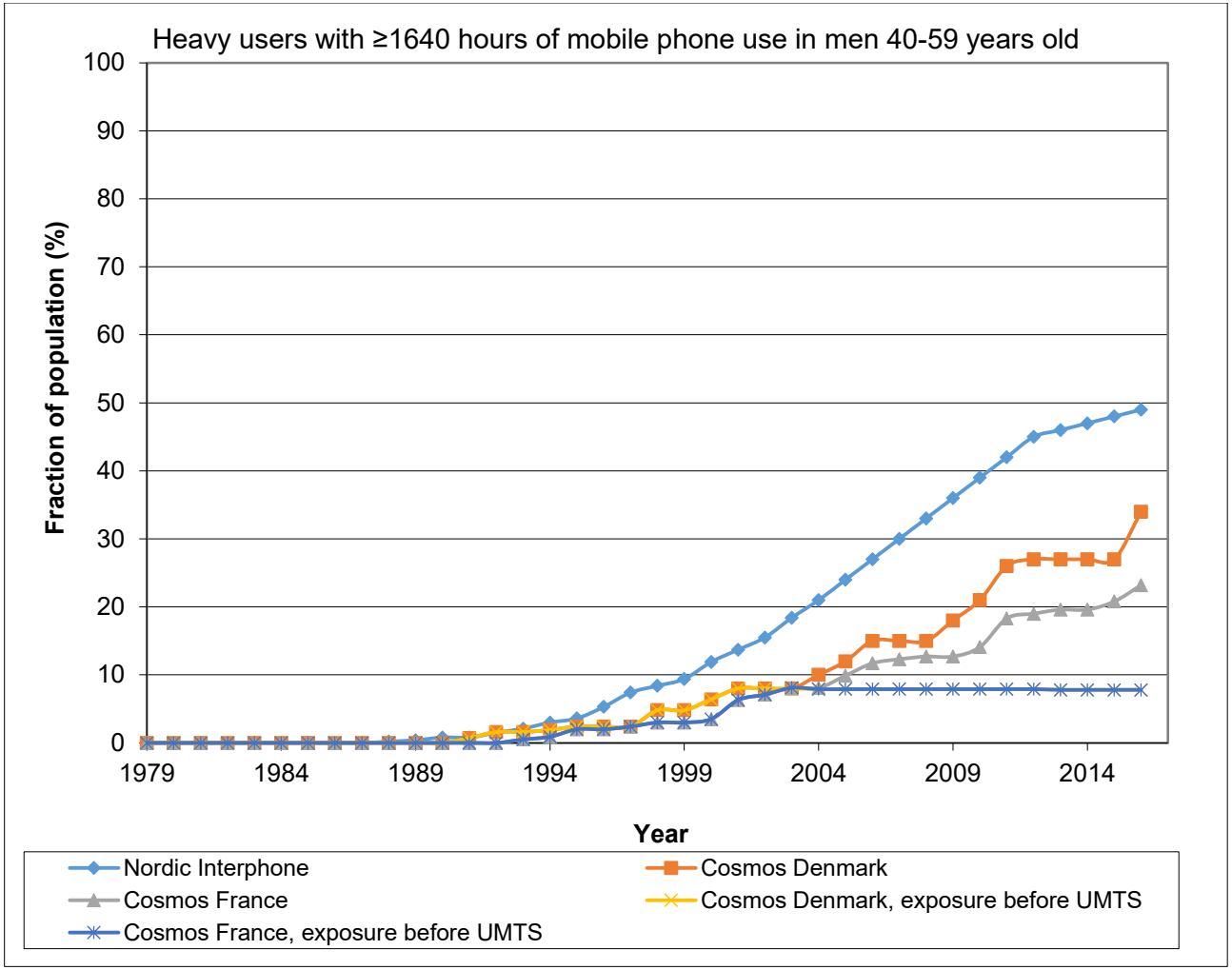

Figure 6: Self-reported prevalence of heavy use, defined as accumulated lifetime conversation time of more than 1640 hours of use among men aged 40-59 years old interviewed in the Nordic countries as Interphone study's controls in 2001-2003, interviewed for the Cosmos study in Denmark in 2007-2009, and interviewed for the Cosmos study in France in 2019. The exposure situation characterised by 1640 hours of use accumulated before 2003 (approximating GSM but not UMTS /LTE) is also presented.

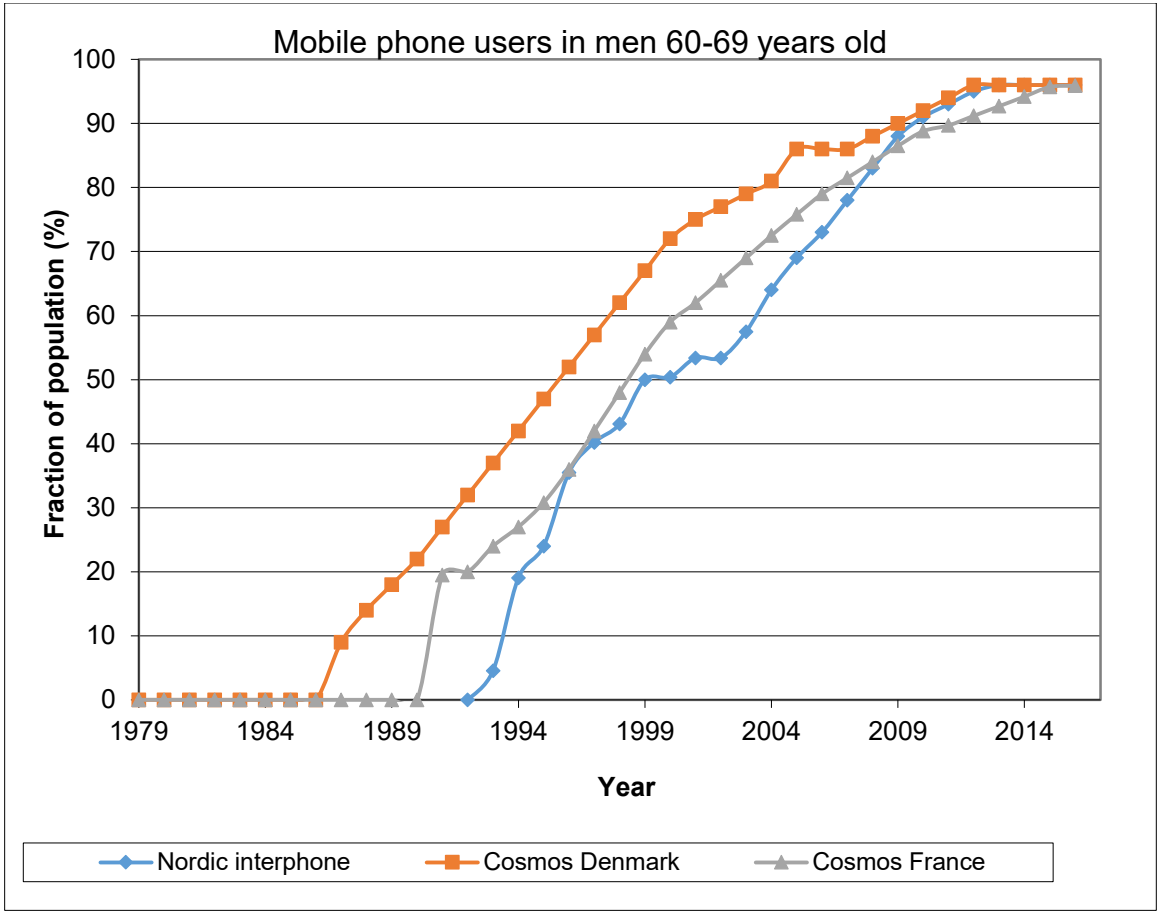

Figure 7: Self-reported prevalence of mobile phone use among men aged 60-69 years old interviewed in the Nordic countries as Interphone study's controls in 2001-2003, interviewed for the Cosmos study in Denmark in 2007-2009, and interviewed for the Cosmos study in France in 2019.

Table 10: Schematic presentation of the set of exposure, the set of risk models, and the set of models for the baseline incidence rate, which together form the risk scenarios studied, for the group of 60-69 years old men.

Subgroup	Source of information on the exposure distribution	Within subgroup, at-risk group	RR	Model of baseline
men 40-59 years old	Assuming exposure in the population equal to that observed in the **Interphone controls** in the **Nordic** countries; in the **Danish** participants of **Cosmos;** in the **French** participants of **Cosmos**	all mobile phone users, no induction period	1.05; 1.08; 1.1; 1.2; 1.3; 1.4; 1.5; 2.0; 2.5	constant baseline rate - power, SIR - half, SIR - 3/4
		all mobile phone users, 5 years induction period		
		all mobile phone users, 10 years induction period		
		all mobile phone users, 15 years induction period		
		all mobile phone users, 20 years induction period		
		>= 339 hours		
		>= 558 hours		
		>= 896 hours		
		>= 1640 hours		
		>= 896 hours before 2003		
		>= 1640 hours before 2003		

*Notes: RR: relative risk; SIR: Standardised Incidence Ratio analysis. On the data from the subgroup of men 40-59, 3 (exposure distributions)*11 (at-risk group definitions) * 9 (relative risk values) * 3 (models for the baseline) = 891 scenarios were analyzed.*

Table 11: Schematic presentation of the set of exposure, the set of risk models, and the set of models for the baseline incidence rate, which together form the risk scenarios studied, for the group of 60-69 years old men.

Subgroup	Source of information on the exposure distribution	Within subgroup, at risk group	RR	Model of baseline
men 60-69	Assuming exposure in the population equal to that observed in the **Danish** participants of **Cosmos;** in the **French** participants of **Cosmos**	all mobile phone users, no induction period	1.05; 1.08; 1.1; 1.2; 1.3; 1.4; 1.5; 2.0; 2.5	SIR - half, SIR - 3/4
		all mobile phone users, 5 years induction period		
		all mobile phone users, 10 years induction period		
		all mobile phone users, 15 years induction period		
		all mobile phone users, 20 years induction period		
		>= 339 hours		
		>= 558 hours		
		>= 896 hours		
		>= 1640 hours		
		>= 896 hours before 2003		
		>= 1640 hours before 2003		

*Notes: RR: relative risk; SIR: Standardised Incidence Ratio analysis. On the data from the subgroup of men 60-69 years old, 3 (exposure distributions)*11 (at-risk group definitions) * 9 (relative risk values) * 2(models for the baseline) = 594 scenarios were analyzed.*

Table 12: RR obtained when fitting Poisson models to the number of cases observed in men aged 40-59 years old when the exposure distributions of mobile phone use (use, with lag or cumulative mobile phone conversation time) obtained from Nordic Interphone controls, Cosmos-Denmark dataset or Cosmos-France datasets are assumed to be the one truly at risk using the simplified statistical model.

Source of exposure distribution	**Nordic controls of Interphone**			**Cosmos-Denmark cohort**			**Cosmos-France cohort**		
At-risk group	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**
All users, no lag	1.06	(1.01-	1.12)	1.06	(1.00-	1.11)	1.06	(1.01-	1.12)
All users, 5 years lag	1.07	(1.01-	1.12)	1.06	(1.01-	1.12)	1.07	(1.01-	1.13)
All users, 10 years lag	1.06	(1.00-	1.11)	1.07	(1.01-	1.13)	1.07	(1.00-	1.14)
All users, 15 years lag	1.05	(0.98-	1.12)	1.06	(1.00-	1.13)	1.06	(0.97-	1.15)
All users, 20 years lag	1.07	(0.93-	1.21)	1.06	(0.96-	1.15)	1.11	(0.92-	1.31)
More than 339 h lifetime use[a]	1.09	(1.01-	1.16)	1.10	(1.01-	1.19)	1.14	(1.01-	1.27)
More than 558 h lifetime use[a]	1.10	(1.01-	1.18)	1.11	(1.00-	1.21)	1.16	(1.00-	1.31)
More than 896 h lifetime use[a]	1.10	(1.01-	1.20)	1.12	(0.99-	1.25)	1.22	(1.01-	1.43)
More than 1640 h lifetime use[a]	1.12	(1.01-	1.23)	1.20	(1.01-	1.39)	1.27	(1.01-	1.54)
More than 896 h lifetime use[a] before 2003	1.24	(1.05-	1.43)	1.39	(1.07-	1.72)	1.52	(1.12-	1.91)
More than 1640 h lifetime use[a] before 2003	1.39	(1.09-	1.68)	1.75	(1.17-	2.33)	1.73	(1.16-	2.30)

Notes: RR: relative risk; LCI: Lower bound of 95% Confidence Interval, UCI: Upper bound of 95% Confidence Interval, a: cumulative mobile phone conversation time with no lag.

Table 13: RR obtained when fitting Poisson models to the observed data of men aged 60-69 when the exposure described in the literature is assumed to be the one truly at risk using the simplified statistical model.

Source of exposure distribution	**Nordic controls of Interphone**			**Cosmos-Denmark cohort**			**Cosmos-France cohort**		
At-risk group	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**
All users, no lag	1.21	(1.14-	1.28)	1.21	(1.14-	1.29)	1.26	(1.17-	1.35)
All users, 5 years lag	1.21	(1.14-	1.28)	1.22	(1.14-	1.29)	1.28	(1.19-	1.37)
All users, 10 years lag	1.23	(1.15-	1.30)	1.24	(1.16-	1.32)	1.33	(1.22-	1.43)
All users, 15 years lag	1.26	(1.16-	1.35)	1.30	(1.20-	1.39)	1.43	(1.28-	1.58)
All users, 20 years lag	1.40	(1.22-	1.58)	1.39	(1.23-	1.54)	1.54	(1.31-	1.78)
More than 339 h lifetime use[a]	1.61	(1.41-	1.81)	1.74	(1.50-	1.98)	2.01	(1.68-	2.35)
More than 558 h lifetime use[a]	1.81	(1.54-	2.08)	1.88	(1.59-	2.17)	2.19	(1.79-	2.59)
More than 896 h lifetime use[a]	2.14	(1.78-	2.50)	2.31	(1.87-	2.76)	2.59	(2.06-	3.12)
More than 1640 h lifetime use[a]	3.06	(2.37-	3.74)	3.10	(2.38-	3.83)	3.02	(2.34-	3.70)
More than 896 h lifetime use[a] before 2003	2.75	(2.18-	3.32)	3.24	(2.50-	3.98)	3.89	(2.89-	4.90)
More than 1640 h lifetime use[a] before 2003	6.89	(4.74-	9.05)	4.62	(3.42-	5.83)	5.18	(3.75-	6.61)

Notes: RR: relative risk; LCI: lower bound of 95% Confidence Interval, UCI: Upper bound of 95% Confidence Interval, a: cumulative mobile phone conversation time with no lag.

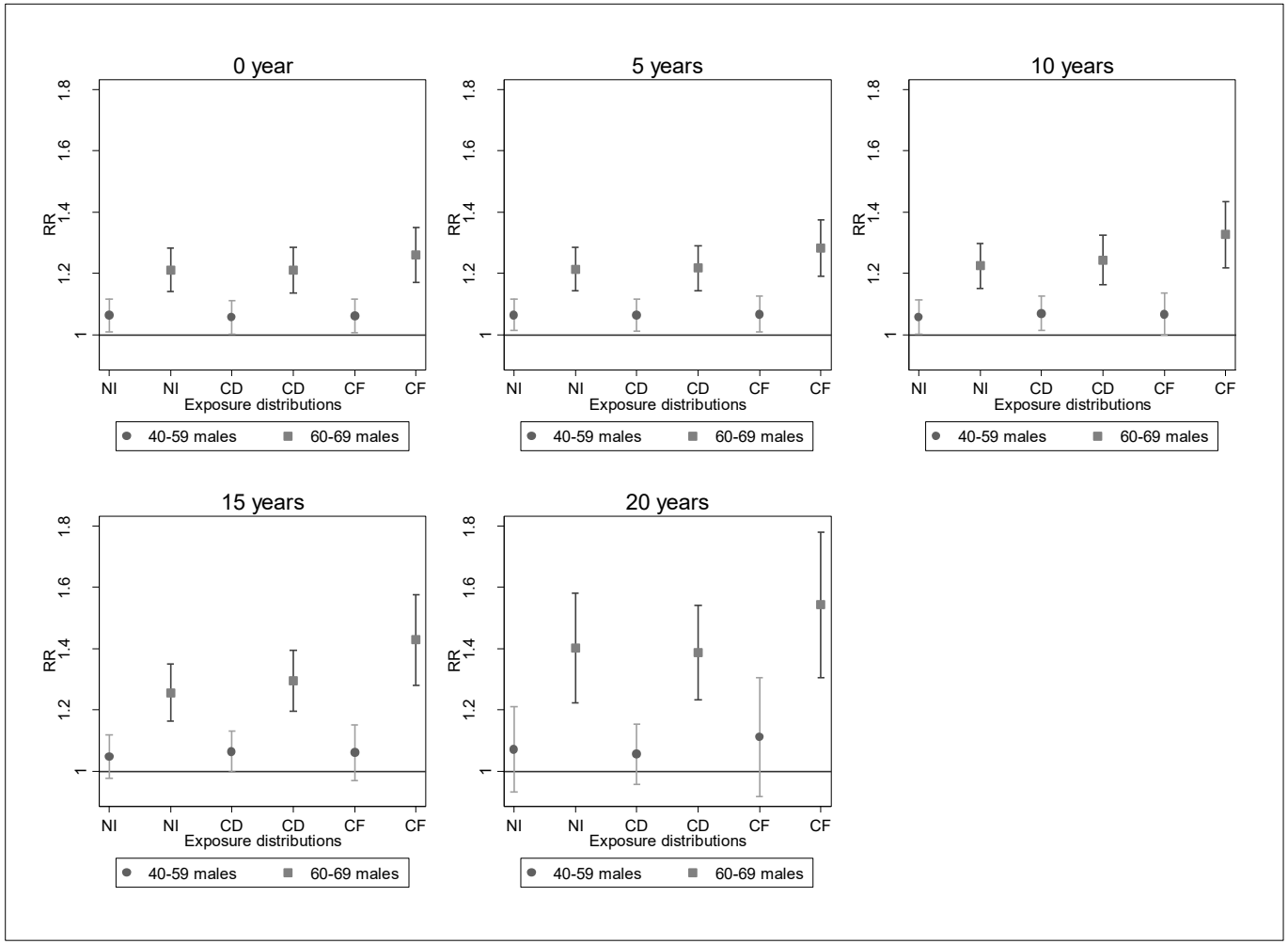

Figure 8: Estimated RR with 95% confidence interval based on observed numbers of cases, exposure distributions in the Nordic Interphone (NI), Cosmos-Denmark (CD) and Cosmos-France (CF) studies, with hypothetical induction periods of 0, 5, 10 (top), 15 and 20 years (bottom), among men aged 40-59 and 60-69 years old.

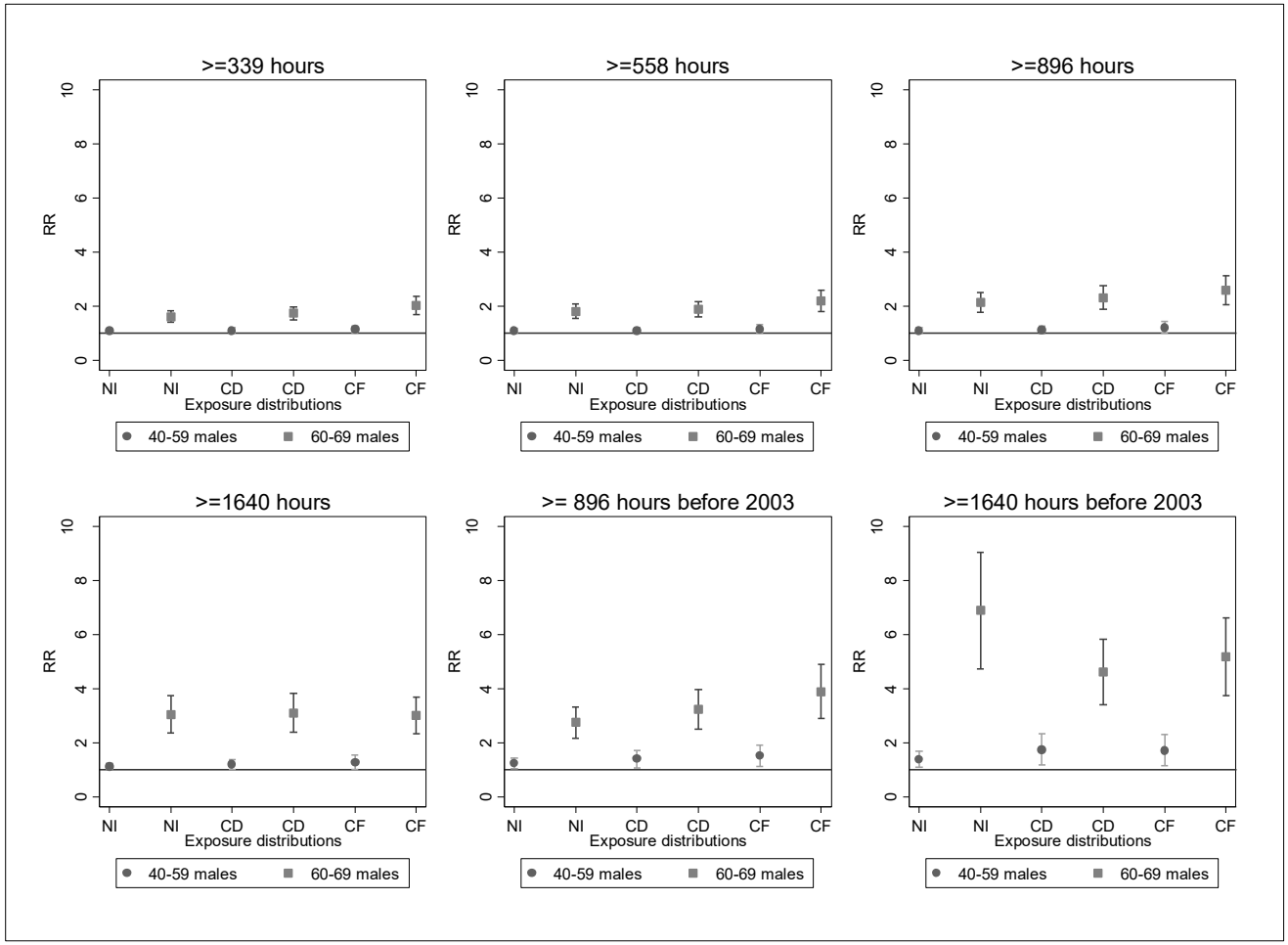

Figure 9: Estimated RR based on observed numbers of cases, exposure distributions in the Nordic Interphone (NI), Cosmos-Denmark (CD) and Cosmos-France (CF) studies, with hypothetical at-risk group those having accumulated at least 339 hours, 558 hours, 896 hours (top), 1640 hours, 896 hours before 2003, and 1640 hours before 2003 (bottom) of mobile phone conversation time with no lag, among men aged 40-59 and 60-69 years old.

Table 14: Power to detect an increased risk in men 40-59 years old in the Nordic countries, based on the simplified statistical model, with various scenarios of risk and the exposure distributions of the Nordic Interphone controls (see text for details).

At-risk population/ Simulated RR	All mobile phone users, no lag	All mobile phone users, 5 yrs lag	All mobile phone users, 10 yrs lag	All mobile phone users, 15 yrs lag	All mobile phone users, 20 yrs lag	User group with >= 339 hrs of use	User group with >= 558 hrs of use	User group with >= 896 hrs of use	User group with >= 1640 hrs of use	User group with >= 896 hrs of use before 2003	User group with >= 1640 hrs of use before 2003
2.5	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
2.0	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
1.5	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	92%
1.4	100%	100%	100%	100%	100%	100%	100%	100%	100%	99%	75%
1.3	100%	100%	100%	100%	98%	100%	100%	100%	100%	88%	48%
1.2	100%	100%	100%	100%	76%	100%	99%	99%	91%	56%	27%
1.1	96%	96%	95%	77%	28%	77%	64%	51%	42%	17%	10%
1.08	86%	88%	79%	54%	17%	61%	43%	38%	28%	11%	7%
1.05	46%	50%	43%	24%	7%	27%	19%	20%	14%	7%	5%

Table 15: Power to detect an increased risk in men 40-59 years old in the Nordic countries, based on the simplified statistical model, with various scenarios of risk and the exposure distributions of the Cosmos-Denmark cohort (see text for details).

At-risk population/ Simulated RR	All mobile phone users, no lag	All mobile phone users, 5 yrs lag	All mobile phone users, 10 yrs lag	All mobile phone users, 15 yrs lag	All mobile phone users, 20 yrs lag	User group with >= 339 hrs of use	User group with >= 558 hrs of use	User group with >= 896 hrs of use	User group with >= 1640 hrs of use	User group with >= 896 hrs of use before 2003	User group with >= 1640 hrs of use before 2003
2.5	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
2.0	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	91%
1.5	100%	100%	100%	100%	100%	100%	100%	100%	100%	87%	39%
1.4	100%	100%	100%	100%	100%	100%	100%	100%	98%	66%	30%
1.3	100%	100%	100%	100%	100%	100%	100%	99%	83%	43%	19%
1.2	100%	100%	100%	100%	96%	99%	96%	84%	48%	21%	9%
1.1	92%	96%	93%	80%	47%	58%	46%	31%	15%	8%	6%
1.08	81%	85%	82%	60%	33%	42%	30%	23%	10%	6%	5%
1.05	40%	46%	43%	30%	18%	19%	16%	10%	8%	5%	4%

Table 16: Power to detect an increased risk in men 40-59 years old in the Nordic countries, based on the simplified statistical model, with various scenarios of risk and the exposure distributions of the Cosmos-France cohort (see text for details).

At-risk population/ Simulated RR	All mobile phone users, no lag	All mobile phone users, 5 yrs lag	All mobile phone users, 10 yrs lag	All mobile phone users, 15 yrs lag	All mobile phone users, 20 yrs lag	User group with >= 339 hrs of use	User group with >= 558 hrs of use	User group with >= 896 hrs of use	User group with >= 1640 hrs of use	User group with >= 896 hrs of use before 2003	User group with >= 1640 hrs of use before 2003
2.5	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
2.0	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	93%
1.5	100%	100%	100%	100%	100%	100%	100%	99%	94%	68%	40%
1.4	100%	100%	100%	100%	97%	100%	100%	96%	84%	52%	27%
1.3	100%	100%	100%	100%	82%	99%	97%	83%	60%	28%	16%
1.2	100%	100%	100%	99%	48%	85%	70%	45%	31%	15%	9%
1.1	94%	92%	81%	54%	16%	31%	22%	17%	10%	8%	5%
1.08	78%	78%	62%	40%	11%	20%	16%	10%	7%	5%	5%
1.05	43%	38%	28%	19%	6%	11%	9%	7%	4%	4%	3%

Table 17: SIR analysis in men 40-59 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls; half of the baseline increase unexplained.

	All mobile phone users, no lag			**All mobile phone users, 5 yrs lag**			**All mobile phone users, 10 yrs lag**			**All mobile phone users, 15 yrs lag**			**All mobile phone users, 20 yrs lag**		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.55	(0.54	; 0.56)	0.60	(0.59	; 0.62)	0.69	(0.67	; 0.70)	0.79	(0.78	; 0.81)	0.91	(0.90	; 0.93)
2.0	0.64	(0.63	; 0.66)	0.70	(0.69	; 0.71)	0.77	(0.76	; 0.78)	0.85	(0.84	; 0.87)	0.94	(0.93	; 0.96)
1.5	0.79	(0.77	; 0.80)	0.83	(0.81	; 0.84)	0.87	(0.86	; 0.89)	0.93	(0.91	; 0.94)	0.98	(0.96	; 1.00)
1.4	0.82	(0.81	; 0.84)	0.86	(0.84	; 0.87)	0.90	(0.88	; 0.92)	0.94	(0.92	; 0.96)	**0.98**	**(0.96**	; **1.00)**
1.3	0.86	(0.85	; 0.88)	0.89	(0.88	; 0.91)	0.92	(0.91	; 0.94)	0.96	(0.94	; 0.98)	**0.99**	**(0.97**	; **1.01)**
1.2	0.91	(0.89	; 0.93)	0.93	(0.91	; 0.95)	0.95	(0.93	; 0.97)	0.98	(0.96	; 0.99)	**1.00**	**(0.98**	; **1.02)**
1.1	0.96	(0.94	; 0.98)	0.97	(0.95	; 0.99)	0.98	(0.96	; 1.00)	**0.99**	**(0.97**	; **1.01)**	**1.00**	**(0.99**	; **1.02)**
1.08	0.97	(0.95	; 0.99)	0.98	(0.96	; 1.00)	**0.99**	**(0.97**	; **1.01)**	**1.00**	**(0.98**	; **1.02)**	**1.01**	**(0.99**	; **1.03)**
1.05	**0.98**	**(0.97**	; **1.00)**	**0.99**	**(0.97**	; **1.01)**	**1.00**	**(0.98**	; **1.02)**	**1.00**	**(0.98**	; **1.02)**	**1.01**	**(0.99**	; **1.03)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non significant SIR indicating compatibility of the expected values with the observed data.

Table 18: SIR analysis in men 40-59 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls, at-risk group is heavy users; half of the baseline increase unexplained.

At-risk population	**User group with >= 339 hrs of use**			**User group with >= 558 hrs of use**			**User group with >= 896 hours**			**User group with >= 1640 hours**			**User group with >= 896 hours before 2003**			**User group with >= 1640 hours before 2003**		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.67	(0.66	; 0.69)	0.72	(0.71	; 0.73)	0.75	(0.74	; 0.77)	0.80	(0.79	; 0.82)	0.84	(0.82	; 0.85)	0.89	(0.88	; 0.91)
2.0	0.76	(0.74	; 0.77)	0.80	(0.78	; 0.81)	0.82	(0.81	; 0.84)	0.86	(0.85	; 0.88)	0.89	(0.87	; 0.90)	0.93	(0.91	; 0.95)
1.5	0.87	(0.85	; 0.88)	0.89	(0.87	; 0.91)	0.91	(0.89	; 0.92)	0.93	(0.91	; 0.95)	0.95	(0.93	; 0.96)	0.97	(0.95	; 0.99)
1.4	0.89	(0.88	; 0.91)	0.91	(0.90	; 0.93)	0.93	(0.91	; 0.94)	0.95	(0.93	; 0.96)	0.96	(0.94	; 0.98)	0.98	(0.96	; 1.00)
1.3	0.92	(0.90	; 0.94)	0.94	(0.92	; 0.95)	0.95	(0.93	; 0.96)	0.96	(0.94	; 0.98)	0.97	(0.95	; 0.99)	**0.99**	**(0.97**	; **1.00)**
1.2	0.95	(0.93	; 0.97)	0.96	(0.94	; 0.98)	0.97	(0.95	; 0.99)	0.98	(0.96	; 1.00)	**0.98**	**(0.97**	; **1.00)**	**0.99**	**(0.98**	; **1.01)**
1.1	0.98	(0.96	; 1.00)	**0.99**	**(0.97**	; **1.00)**	**0.99**	**(0.97**	; **1.01)**	**0.99**	**(0.98**	; **1.01)**	**1.00**	**(0.98**	; **1.02)**	**1.00**	**(0.98**	; **1.02)**
1.08	**0.99**	**(0.97**	; **1.00)**	**0.99**	**(0.97**	; **1.01)**	**0.99**	**(0.97**	; **1.01)**	**1.00**	**(0.98**	; **1.02)**	**1.00**	**(0.98**	; **1.02)**	**1.00**	**(0.99**	; **1.02)**
1.05	**1.00**	**(0.98**	; **1.01)**	**1.00**	**(0.98**	; **1.02)**	**1.00**	**(0.98**	; **1.02)**	**1.00**	**(0.98**	; **1.02)**	**1.00**	**(0.99**	; **1.02)**	**1.01**	**(0.99**	; **1.03)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non significant SIR indicating compatibility of the expected values with the observed data.

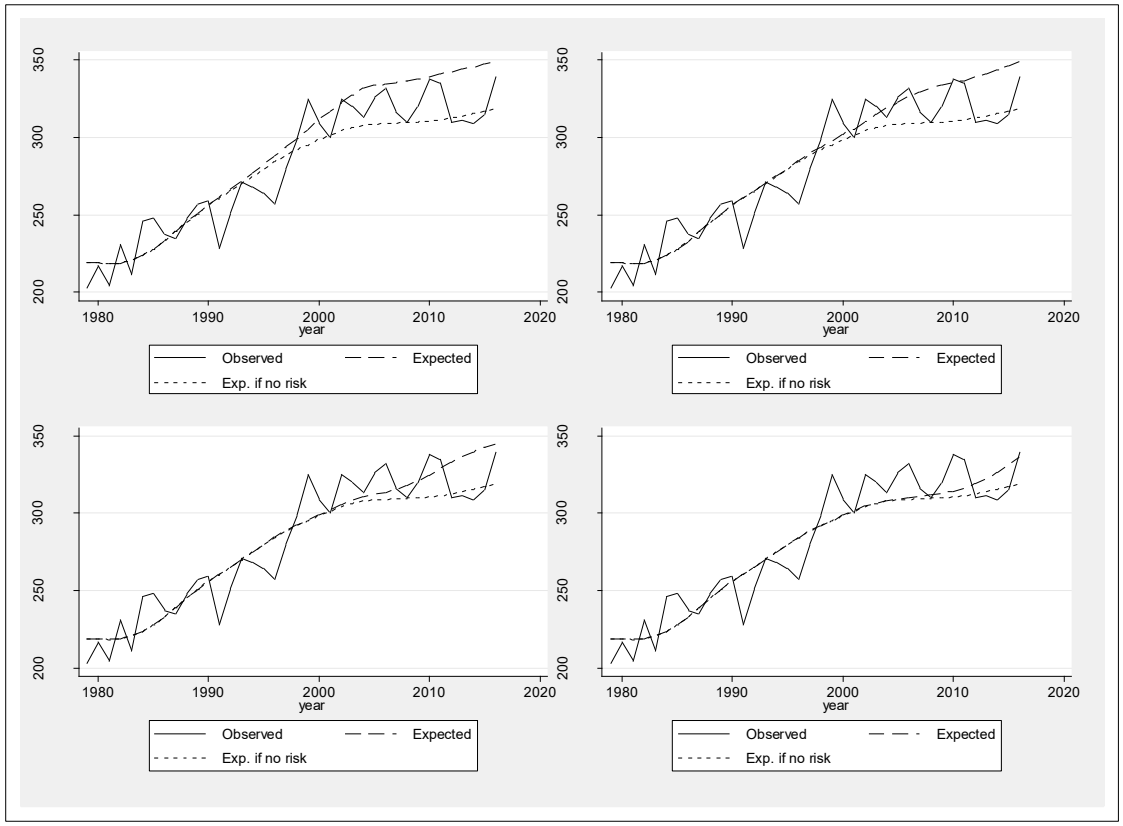

Figure 10 Graphical illustration of SIR analyses. Graphs of observed numbers of cases and expected number of cases over time when half of the baseline increase explained by the mobile phone related risk and the other half unexplained, for scenarios of exposure based on the Nordic Interphone controls male 40-59 years old, with a RR of 1.1, and 5 (top left), 10 (top right), 15 (low left), and 20 (low right) years of lag time. Observed (respectively Expected) indicates the observed (respectively expected) number of cases, and "Exp. if no risk" indicates the expected number of cases if the RR was equal to 1. The expected number of cases were statistically significantly different and higher from the observed number of cases in the upper panel, and were not statistically significantly different in the lower panels (Table 17, line 7). It can be seen that towards the end of the period of observation, the expected number of cases was higher than the observed for the upper panels, while observed and expected aligned better in the lower panels.

Table 19: SIR analysis in men 40-59 years old under the assumption that the exposure in the population is equal to that observed in the Danish participants of Cosmos; half of the baseline increase unexplained.

At-risk population	All mobile phone users, no lag			All mobile phone users, 5 yrs lag			All mobile phone users, 10 yrs lag			All mobile phone users, 15 yrs lag			All mobile phone users, 20 yrs lag		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.52	(0.51	; 0.53)	0.58	(0.57	; 0.59)	0.65	(0.64	; 0.67)	0.75	(0.74	; 0.76)	0.86	(0.84	; 0.87)
2.0	0.62	(0.61	; 0.64)	0.68	(0.66	; 0.69)	0.74	(0.73	; 0.76)	0.82	(0.81	; 0.84)	0.90	(0.89	; 0.92)
1.5	0.77	(0.76	; 0.79)	0.81	(0.79	; 0.83)	0.86	(0.84	; 0.87)	0.91	(0.89	; 0.92)	0.95	(0.94	; 0.97)
1.4	0.81	(0.79	; 0.83)	0.84	(0.83	; 0.86)	0.88	(0.87	; 0.90)	0.93	(0.91	; 0.94)	0.97	(0.95	; 0.98)
1.3	0.85	(0.84	; 0.87)	0.88	(0.86	; 0.90)	0.91	(0.89	; 0.93)	0.95	(0.93	; 0.96)	**0.98**	**(0.96**	**; 1.00)**
1.2	0.90	(0.88	; 0.92)	0.92	(0.90	; 0.94)	0.94	(0.93	; 0.96)	0.97	(0.95	; 0.99)	**0.99**	**(0.97**	**; 1.01)**
1.1	0.95	(0.93	; 0.97)	0.96	(0.95	; 0.98)	0.98	(0.96	; 0.99)	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**
1.08	0.96	(0.95	; 0.98)	0.97	(0.95	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**
1.05	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 20: SIR analysis in men 40-59 years old under the assumption that the exposure in the population is equal to that observed in the Danish participants of Cosmos, at-risk group are heavy users; half of the baseline increase unexplained.

At-risk population	User group with >= 339 hrs of use			User group with >= 558 hrs of use			User group with >= 896 hours			User group with >= 1640 hours			User group with >= 896 hours before 2003			User group with >= 1640 hours before 2003		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.74	(0.73	; 0.76)	0.78	(0.77	; 0.80)	0.83	(0.81	; 0.84)	0.88	(0.87	; 0.90)	0.90	(0.88	; 0.92)	0.95	(0.93	; 0.97)
2.0	0.81	(0.80	; 0.83)	0.85	(0.83	; 0.86)	0.88	(0.87	; 0.90)	0.92	(0.91	; 0.94)	0.93	(0.92	; 0.95)	0.97	(0.95	; 0.99)
1.5	0.90	(0.89	; 0.92)	0.92	(0.90	; 0.94)	0.94	(0.92	; 0.96)	0.97	(0.95	; 0.98)	0.97	(0.95	; 0.99)	**0.99**	**(0.97**	**; 1.01)**
1.4	0.92	(0.91	; 0.94)	0.94	(0.92	; 0.96)	0.96	(0.94	; 0.97)	0.97	(0.96	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.98**	**; 1.01)**
1.3	0.94	(0.93	; 0.96)	0.96	(0.94	; 0.97)	0.97	(0.95	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**
1.2	0.97	(0.95	; 0.98)	0.97	(0.96	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**
1.1	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**
1.08	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.99**	**; 1.02)**	**1.01**	**(0.99**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**
1.05	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.99**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.03)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 21: SIR analysis in men 40-59 years old under the assumption that the exposure in the population is equal to that observed in the French participants of Cosmos; half of the baseline increase unexplained.

At-risk population	**All mobile phone users, no lag**			**All mobile phone users, 5 yrs lag**			**All mobile phone users, 10 yrs lag**			**All mobile phone users, 15 yrs lag**			**All mobile phone users, 20 yrs lag**		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.58	(0.57	; 0.60)	0.65	(0.64	; 0.67)	0.74	(0.73	; 0.76)	0.84	(0.82	; 0.85)	0.94	(0.92	; 0.96)
2.0	0.68	(0.67	; 0.69)	0.74	(0.73	; 0.76)	0.81	(0.80	; 0.83)	0.89	(0.87	; 0.91)	0.96	(0.95	; 0.98)
1.5	0.81	(0.80	; 0.83)	0.86	(0.84	; 0.87)	0.90	(0.89	; 0.92)	0.95	(0.93	; 0.96)	**0.99**	**(0.97**	**; 1.01)**
1.4	0.85	(0.83	; 0.86)	0.88	(0.87	; 0.90)	0.92	(0.90	; 0.94)	0.96	(0.94	; 0.98)	**0.99**	**(0.97**	**; 1.01)**
1.3	0.88	(0.87	; 0.90)	0.91	(0.89	; 0.93)	0.94	(0.93	; 0.96)	0.97	(0.95	; 0.99)	**1.00**	**(0.98**	**; 1.02)**
1.2	0.92	(0.90	; 0.94)	0.94	(0.93	; 0.96)	0.96	(0.95	; 0.98)	**0.98**	**(0.97**	**; 1.00)**	**1.00**	**(0.98**	**; 1.02)**
1.1	0.96	(0.95	; 0.98)	0.98	(0.96	; 0.99)	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**
1.08	0.97	(0.96	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**
1.05	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.99**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 22: SIR Analysis in men 40-59 years old assuming exposure in the population equal to that observed in the French participants of Cosmos, at-risk group are heavy users ; half of the baseline increase unexplained.

At-risk population	User group with >= 339 hrs of use			User group with >= 558 hrs of use			User group with >= 896 hours			User group with >= 1640 hours			User group with >= 896 hours before 2003			User group with >= 1640 hours before 2003		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.81	(0.80	; 0.83)	0.85	(0.83	; 0.86)	0.88	(0.87	; 0.90)	0.91	(0.90	; 0.93)	0.92	(0.91	; 0.94)	0.95	(0.93	; 0.97)
2.0	0.87	(0.85	; 0.88)	0.90	(0.88	; 0.91)	0.92	(0.90	; 0.94)	0.94	(0.93	; 0.96)	0.95	(0.93	; 0.97)	0.97	(0.95	; 0.99)
1.5	0.93	(0.92	; 0.95)	0.95	(0.93	; 0.97)	0.96	(0.95	; 0.98)	**0.98**	**(0.96**	**; 1.00)**	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**
1.4	0.95	(0.93	; 0.97)	0.96	(0.94	; 0.98)	0.97	(0.96	; 0.99)	**0.98**	**(0.97**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.01)**
1.3	0.96	(0.95	; 0.98)	0.97	(0.96	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**
1.2	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**
1.1	**1.00**	**(0.98**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.99**	**; 1.02)**	**1.01**	**(0.99**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**
1.08	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.03)**
1.05	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.99**	**; 1.02)**	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.03)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 23: SIR analysis in men 60-69 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls; half of the baseline increase unexplained.

At-risk population	All mobile phone users, no lag			All mobile phone users, 5 yrs lag			All mobile phone users, 10 yrs lag			All mobile phone users, 15 yrs lag			All mobile phone users, 20 yrs lag		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.64	(0.62	; 0.65)	0.68	(0.67	; 0.70)	0.73	(0.72	; 0.75)	0.84	(0.82	; 0.86)	0.97	(0.95	; 0.99)
2.0	0.74	(0.72	; 0.76)	0.78	(0.76	; 0.80)	0.83	(0.81	; 0.84)	0.91	(0.89	; 0.93)	**1.01**	**(0.99**	; **1.03)**
1.5	0.89	(0.87	; 0.91)	0.91	(0.89	; 0.93)	0.94	(0.92	; 0.96)	**0.99**	**(0.97**	; **1.02)**	1.05	(1.03	; 1.08)
1.4	0.92	(0.90	; 0.94)	0.94	(0.92	; 0.97)	0.97	(0.95	; 0.99)	**1.01**	**(0.99**	; **1.04)**	1.06	(1.04	; 1.09)
1.3	0.96	(0.94	; 0.98)	**0.98**	**(0.96**	; **1.00)**	**1.00**	**(0.98**	; **1.02)**	1.03	(1.01	; 1.06)	1.07	(1.05	; 1.10)
1.2	**1.00**	**(0.98**	; **1.03)**	**1.02**	**(0.99**	; **1.04)**	1.03	(1.01	; 1.05)	1.05	(1.03	; 1.08)	1.08	(1.06	; 1.10)
1.1	1.05	(1.02	; 1.07)	1.06	(1.03	; 1.08)	1.06	(1.04	; 1.09)	1.08	(1.05	; 1.10)	1.09	(1.07	; 1.11)
1.08	1.06	(1.03	; 1.08)	1.06	(1.04	; 1.09)	1.07	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.07	; 1.12)
1.05	1.07	(1.05	; 1.10)	1.08	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 24: SIR analysis in men 60-69 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls, at-risk group is heavy users; half of the baseline increase unexplained.

At-risk population	User group with >= 339 hrs of use			User group with >= 558 hrs of use			User group with >= 896 hours			User group with >= 1640 hours			User group with >= 896 hours before 2003			User group with >= 1640 hours before 2003		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.89	(0.87	; 0.91)	0.94	(0.92	; 0.96)	**0.98**	**(0.95**	**; 1.00)**	1.04	(1.01	; 1.06)	**1.01**	**(0.99**	**; 1.03)**	1.07	(1.05	; 1.10)
2.0	0.95	(0.93	; 0.97)	**0.99**	**(0.97**	**; 1.01)**	**1.01**	**(0.99**	**; 1.04)**	1.06	(1.03	; 1.08)	1.04	(1.02	; 1.06)	1.08	(1.06	; 1.11)
1.5	**1.02**	**(1.00**	**; 1.04)**	1.04	(1.02	; 1.06)	1.05	(1.03	; 1.08)	1.08	(1.05	; 1.10)	1.07	(1.04	; 1.09)	1.09	(1.07	; 1.11)
1.4	1.03	(1.01	; 1.06)	1.05	(1.03	; 1.08)	1.06	(1.04	; 1.09)	1.08	(1.06	; 1.11)	1.07	(1.05	; 1.10)	1.09	(1.07	; 1.12)
1.3	1.05	(1.03	; 1.07)	1.06	(1.04	; 1.09)	1.07	(1.05	; 1.10)	1.09	(1.06	; 1.11)	1.08	(1.06	; 1.10)	1.09	(1.07	; 1.12)
1.2	1.07	(1.04	; 1.09)	1.07	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.07	; 1.12)	1.09	(1.06	; 1.11)	1.10	(1.07	; 1.12)
1.1	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.11)	1.09	(1.07	; 1.12)	1.09	(1.07	;1.12)	1.10	(1.07	; 1.12)
1.08	1.09	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)
1.05	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 25: SIR Analysis among men aged 60-69 years old, assuming exposure in the population equal to that observed in the Danish participants of Cosmos; half of the baseline increase unexplained.

At-risk population	All mobile phone users, no lag			All mobile phone users, 5 yrs lag			All mobile phone users, 10 yrs lag			All mobile phone users, 15 yrs lag			All mobile phone users, 20 yrs lag		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.60	(0.59	; 0.62)	0.66	(0.64	; 0.67)	0.73	(0.71	; 0.75)	0.83	(0.81	; 0.85)	0.95	(0.93	; 0.97)
2.0	0.71	(0.69	; 0.72)	0.76	(0.74	; 0.78)	0.82	(0.80	; 0.84)	0.90	(0.88	; 0.92)	**0.99**	**(0.97**	**; 1.02)**
1.5	0.86	(0.84	; 0.88)	0.90	(0.88	; 0.92)	0.94	(0.92	; 0.96)	**0.99**	**(0.97**	**; 1.01)**	1.04	(1.02	; 1.07)
1.4	0.90	(0.88	; 0.92)	0.93	(0.91	; 0.95)	0.97	(0.95	; 0.99)	**1.01**	**(0.99**	**; 1.03)**	1.05	(1.03	; 1.08)
1.3	0.94	(0.92	; 0.96)	0.97	(0.95	; 0.99)	**1.00**	**(0.98**	**; 1.02)**	1.03	(1.01	; 1.06)	1.06	(1.04	; 1.09)
1.2	**0.99**	**(0.97**	**; 1.01)**	**1.01**	**(0.99**	**; 1.03)**	1.03	(1.01	; 1.05)	1.05	(1.03	; 1.08)	1.08	(1.05	; 1.10)
1.1	1.04	(1.02	; 1.07)	1.05	(1.03	; 1.08)	1.06	(1.04	; 1.09)	1.08	(1.05	; 1.10)	1.09	(1.06	; 1.11)
1.08	1.05	(1.03	; 1.08)	1.06	(1.04	; 1.09)	1.07	(1.05	; 1.09)	1.08	(1.06	; 1.11)	1.09	(1.07	; 1.11)
1.05	1.07	(1.05	; 1.09)	1.07	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 26: SIR analysis in men 60-69 years old under the assumption that the exposure in the population is equal to that observed in the Danish participants of Cosmos, at-risk group is heavy users; half of the baseline increase unexplained.

At-risk population	**User group with >= 339 hrs of use**			**User group with >= 558 hrs of use**			**User group with >= 896 hours**			**User group with >= 1640 hours**			**User group with >= 896 hours before 2003**			**User group with >= 1640 hours before 2003**		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.92	(0.90	; 0.94)	0.96	(0.93	; 0.98)	**1.01**	**(0.98**	**; 1.03)**	1.04	(1.02	; 1.07)	1.03	(1.01	; 1.05)	1.06	(1.03	; 1.08)
2.0	0.97	(0.95	; 0.99)	**1.00**	**(0.98**	**; 1.02)**	1.04	(1.01	; 1.06)	1.06	(1.04	; 1.08)	1.05	(1.03	; 1.08)	1.07	(1.05	; 1.10)
1.5	1.03	(1.01	; 1.06)	1.05	(1.02	; 1.07)	1.07	(1.04	; 1.09)	1.08	(1.06	; 1.10)	1.08	(1.05	; 1.10)	1.09	(1.06	; 1.11)
1.4	1.04	(1.02	; 1.07)	1.06	(1.03	; 1.08)	1.07	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.08	(1.06	; 1.10)	1.09	(1.06	; 1.11)
1.3	1.06	(1.03	; 1.08)	1.07	(1.04	; 1.09)	1.08	(1.05	; 1.10)	1.09	(1.06	; 1.11)	1.08	(1.06	; 1.11)	1.09	(1.07	; 1.12)
1.2	1.07	(1.05	; 1.10)	1.08	(1.05	; 1.10)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.11)	1.09	(1.07	; 1.12)
1.1	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)
1.08	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)
1.05	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 27: SIR Analysis among men aged 60-69 years old, assuming exposure in the population equal to that observed in the French participants of Cosmos; half of the baseline increase unexplained.

At-risk population	All mobile phone users, no lag			All mobile phone users, 5 yrs lag			All mobile phone users, 10 yrs lag			All mobile phone users, 15 yrs lag			All mobile phone users, 20 yrs lag		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.69	(0.67	; 0.71)	0.76	(0.75	; 0.78)	0.84	(0.82	; 0.85)	0.91	(0.89	; 0.93)	**1.01**	**(0.99**	**; 1.03)**
2.0	0.79	(0.77	; 0.81)	0.85	(0.83	; 0.87)	0.91	(0.89	; 0.93)	0.97	(0.95	; 0.99)	**1.04**	**(1.01**	**; 1.06)**
1.5	0.92	(0.90	; 0.94)	0.96	(0.94	; 0.98)	**0.99**	**(0.97**	**; 1.02)**	1.03	(1.01	; 1.05)	1.07	(1.04	; 1.09)
1.4	0.95	(0.93	; 0.97)	**0.98**	**(0.96**	**; 1.01)**	**1.01**	**(0.99**	**; 1.04)**	1.04	(1.02	; 1.07)	1.07	(1.05	; 1.10)
1.3	**0.98**	**(0.96**	**; 1.00)**	**1.01**	**(0.99**	**; 1.03)**	1.03	(1.01	; 1.06)	1.06	(1.03	; 1.08)	1.08	(1.06	; 1.10)
1.2	**1.02**	**(1.00**	**; 1.04)**	1.04	(1.01	; 1.06)	1.05	(1.03	; 1.08)	1.07	(1.05	; 1.09)	1.09	(1.06	; 1.11)
1.1	1.06	(1.03	; 1.08)	1.07	(1.04	; 1.09)	1.08	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.07	; 1.12)
1.08	1.07	(1.04	; 1.09)	1.07	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)
1.05	1.08	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 28: SIR analysis in men 60-69 years old under the assumption that the exposure in the population is equal to that observed in the French participants of Cosmos, at-risk group is heavy users; half of the baseline increase unexplained.

At-risk population	**User group with >= 339 hrs of use**			**User group with >= 558 hrs of use**			**User group with >= 896 hours**			**User group with >= 1640 hours**			**User group with >= 896 hours before 2003**			**User group with >= 1640 hours before 2003**		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.97	(0.95	; 0.99)	**0.99**	**(0.97**	**; 1.02)**	**1.02**	**(0.99**	**; 1.04)**	1.04	(1.01	; 1.06)	1.05	(1.02	; 1.07)	1.06	(1.04	; 1.09)
2.0	**1.01**	**(0.99**	**; 1.03)**	1.03	(1.00	; 1.05)	1.04	(1.02	; 1.07)	1.06	(1.03	; 1.08)	1.06	(1.04	; 1.09)	1.08	(1.05	; 1.10)
1.5	1.05	(1.03	; 1.08)	1.06	(1.04	; 1.09)	1.07	(1.05	; 1.09)	1.08	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)
1.4	1.06	(1.04	; 1.09)	1.07	(1.04	; 1.09)	1.08	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.08	(1.06	; 1.11)	1.09	(1.07	; 1.11)
1.3	1.07	(1.05	; 1.09)	1.08	(1.05	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)
1.2	1.08	(1.06	; 1.10)	1.08	(1.06	; 1.11)	1.09	(1.06	; 1.11)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)
1.1	1.09	(1.07	; 1.11)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)
1.08	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)
1.05	1.09	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)	1.10	(1.07	; 1.12)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 29: SIR analysis in men 40-59 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls; 75% of the baseline increase unexplained.

At-risk population	All mobile phone users, no lag			All mobile phone users, 5 yrs lag			All mobile phone users, 10 yrs lag			All mobile phone users, 15 yrs lag			All mobile phone users, 20 yrs lag		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.54	(0.53	; 0.55)	0.60	(0.59	; 0.61)	0.68	(0.67	; 0.69)	0.79	(0.77	; 0.80)	0.91	(0.89	; 0.92)
2.0	0.64	(0.63	; 0.65)	0.69	(0.68	; 0.71)	0.76	(0.75	; 0.78)	0.85	(0.83	; 0.86)	0.94	(0.92	; 0.95)
1.5	0.78	(0.77	; 0.80)	0.82	(0.80	; 0.83)	0.87	(0.85	; 0.88)	0.92	(0.90	; 0.94)	0.97	(0.95	; 0.99)
1.4	0.82	(0.80	; 0.83)	0.85	(0.83	; 0.87)	0.89	(0.87	; 0.91)	0.93	(0.92	; 0.95)	0.98	(0.96	; 0.99)
1.3	0.86	(0.84	; 0.87)	0.88	(0.87	; 0.90)	0.92	(0.90	; 0.93)	0.95	(0.93	; 0.97)	**0.98**	**(0.96**	**; 1.00)**
1.2	0.90	(0.88	; 0.92)	0.92	(0.90	; 0.94)	0.94	(0.93	; 0.96)	0.97	(0.95	; 0.99)	**0.99**	**(0.97**	**; 1.01)**
1.1	0.95	(0.93	; 0.97)	0.96	(0.94	; 0.98)	0.97	(0.95	; 0.99)	**0.99**	**(0.97**	**; 1.00)**	**1.00**	**(0.98**	**; 1.02)**
1.08	0.96	(0.94	; 0.98)	0.97	(0.95	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**
1.05	0.98	(0.96	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.98**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 30: SIR analysis in men 40-59 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls, at-risk group is heavy users; 75% of the baseline increase unexplained.

At-risk population	**User group with >= 339 hrs of use**			**User group with >= 558 hrs of use**			**User group with >= 896 hours**			**User group with >= 1640 hours**			**User group with >= 896 hours before 2003**			**User group with >= 1640 hours before 2003**		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.67	(0.65	; 0.68)	0.71	(0.70	; 0.73)	0.75	(0.73	; 0.76)	0.80	(0.78	; 0.81)	0.83	(0.81	; 0.84)	0.89	(0.87	; 0.90)
2.0	0.75	(0.74	; 0.77)	0.79	(0.77	; 0.80)	0.82	(0.80	; 0.83)	0.85	(0.84	; 0.87)	0.88	(0.86	; 0.90)	0.92	(0.91	; 0.94)
1.5	0.86	(0.84	; 0.88)	0.88	(0.87	; 0.90)	0.90	(0.88	; 0.92)	0.92	(0.91	; 0.94)	0.94	(0.92	; 0.96)	0.96	(0.94	; 0.98)
1.4	0.88	(0.87	; 0.90)	0.90	(0.89	; 0.92)	0.92	(0.90	; 0.94)	0.94	(0.92	; 0.96)	0.95	(0.93	; 0.97)	0.97	(0.95	; 0.99)
1.3	0.91	(0.89	; 0.93)	0.93	(0.91	; 0.95)	0.94	(0.92	; 0.96)	0.95	(0.94	; 0.97)	0.96	(0.94	; 0.98)	0.98	(0.96	; 1.00)
1.2	0.94	(0.92	; 0.96)	0.95	(0.93	; 0.97)	0.96	(0.94	; 0.98)	0.97	(0.95	; 0.99)	0.98	(0.96	; 0.99)	**0.99**	**(0.97**	**; 1.00)**
1.1	0.97	(0.95	; 0.99)	0.98	(0.96	; 1.00)	0.98	(0.96	; 1.00)	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.98**	**; 1.01)**
1.08	0.98	(0.96	; 1.00)	**0.98**	**(0.96**	**; 1.00)**	**0.99**	**(0.97**	**; 1.00)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**
1.05	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.97**	**; 1.01)**	**0.99**	**(0.98**	**; 1.01)**	**1.00**	**(0.98**	**; 1.02)**	**1.00**	**(0.98**	**; 1.02)**

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 31: SIR analysis in men 60-69 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls; 75% of the baseline increase unexplained.

At-risk population	All mobile phone users, no lag			All mobile phone users, 5 yrs lag			All mobile phone users, 10 yrs lag			All mobile phone users, 15 yrs lag			All mobile phone users, 20 yrs lag		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.60	(0.59	; 0.62)	0.64	(0.63	; 0.66)	0.70	(0.68	; 0.71)	0.79	(0.78	; 0.81)	0.92	(0.90	; 0.95)
2.0	0.70	(0.69	; 0.72)	0.74	(0.72	; 0.76)	0.78	(0.77	; 0.80)	0.86	(0.84	; 0.88)	0.96	(0.94	; 0.98)
1.5	0.84	(0.82	; 0.86)	0.87	(0.85	; 0.89)	0.90	(0.88	; 0.92)	0.95	(0.93	; 0.97)	**1.00**	**(0.98**	**; 1.03)**
1.4	0.88	(0.86	; 0.90)	0.90	(0.88	; 0.92)	0.92	(0.90	; 0.94)	0.97	(0.94	; 0.99)	**1.01**	**(0.99**	**; 1.04)**
1.3	0.91	(0.89	; 0.93)	0.93	(0.91	; 0.95)	0.95	(0.93	; 0.97)	**0.99**	**(0.96**	**; 1.01)**	**1.02**	**(1.00**	**; 1.04)**
1.2	0.95	(0.93	; 0.98)	0.97	(0.95	; 0.99)	**0.98**	**(0.96**	**; 1.00)**	**1.01**	**(0.98**	**; 1.03)**	1.03	(1.01	; 1.05)
1.1	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.98**	**; 1.03)**	**1.01**	**(0.99**	**; 1.04)**	1.03	(1.00	; 1.05)	1.04	(1.02	; 1.06)
1.08	**1.01**	**(0.99**	**; 1.03)**	**1.01**	**(0.99**	**; 1.04)**	**1.02**	**(1.00**	**; 1.04)**	1.03	(1.01	; 1.05)	1.04	(1.02	; 1.06)
1.05	1.02	(1.00	; 1.05)	1.03	(1.00	; 1.05)	1.03	(1.01	; 1.05)	1.04	(1.01	; 1.06)	1.04	(1.02	; 1.07)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

Table 32: SIR analysis in men 60-69 years old under the assumption that the exposure in the population is equal to that observed in the Nordic Interphone controls, at-risk group is heavy users; 75% of the baseline increase unexplained.

At-risk population	**User group with >= 339 hrs of use**			**User group with >= 558 hrs of use**			**User group with >= 896 hours**			**User group with >= 1640 hours**			**User group with >= 896 hours before 2003**			**User group with >= 1640 hours before 2003**		
Hypothetical RR	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
2.5	0.85	(0.83	; 0.87)	0.89	(0.87	; 0.91)	0.93	(0.91	; 0.95)	**0.99**	**(0.97**	**; 1.01)**	0.96	(0.94	; 0.98)	**1.02**	**(1.00**	**; 1.05)**
2.0	0.90	(0.88	; 0.92)	0.94	(0.92	; 0.96)	0.97	(0.94	; 0.99)	**1.01**	**(0.98**	**; 1.03)**	**0.99**	**(0.97**	**; 1.01)**	1.03	(1.01	; 1.05)
1.5	0.97	(0.95	; 0.99)	**0.99**	**(0.97**	**; 1.01)**	**1.01**	**(0.98**	**; 1.03)**	1.03	(1.00	; 1.05)	**1.02**	**(1.00**	**; 1.04)**	1.04	(1.02	; 1.06)
1.4	**0.99**	**(0.96**	**; 1.01)**	**1.00**	**(0.98**	**; 1.03)**	**1.01**	**(0.99**	**; 1.04)**	1.03	(1.01	; 1.06)	1.02	(1.00	; 1.05)	1.04	(1.02	; 1.06)
1.3	**1.00**	**(0.98**	**; 1.02)**	**1.01**	**(0.99**	**; 1.04)**	**1.02**	**(1.00**	**; 1.05)**	1.04	(1.01	; 1.06)	1.03	(1.01	; 1.05)	1.04	(1.02	; 1.07)
1.2	**1.02**	**(0.99**	**; 1.04)**	1.02	(1.00	; 1.05)	1.03	(1.01	; 1.05)	1.04	(1.02	; 1.06)	1.04	(1.01	; 1.06)	1.04	(1.02	; 1.07)
1.1	1.03	(1.01	; 1.06)	1.04	(1.01	; 1.06)	1.04	(1.02	; 1.06)	1.04	(1.02	; 1.07)	1.04	(1.02	; 1.07)	1.05	(1.02	; 1.07)
1.08	1.04	(1.01	; 1.06)	1.04	(1.02	; 1.06)	1.04	(1.02	; 1.06)	1.04	(1.02	; 1.07)	1.04	(1.02	; 1.07)	1.05	(1.02	; 1.07)
1.05	1.04	(1.02	; 1.06)	1.04	(1.02	; 1.07)	1.04	(1.02	; 1.07)	1.05	(1.02	; 1.07)	1.05	(1.02	; 1.07)	1.05	(1.02	; 1.07)

Notes: RR: relative risk; SIR Standardised incidence ratio; LCI: lower bound of 95% Confidence Interval, UCI: upper bound of 95% Confidence Interval. In bold, non-significant SIR indicating compatibility of the expected values with the observed data.

12 Annex

Annex Table 1: List of morphological codes according to ICD-O classifications for tumours located in the brain, i.e. topographical code C71.x. Note that ICD-7 has different codes.

ICD revision	ICD codes for gliomas	ICD codes for glioblastomas	ICD codes for high grade gliomas
ICD-O-3.2	*9380 to 9460,* *Exclude 9412, 9413*	9440/3, 9441/3, 9442/3, 9445/3	Glioblastomas + 9380/3, 9381/3, 9382/3, 9385/3, 9390/3, 9392/3, 9401/3, 9451/3, 9460/3
ICD-O-3.1	*9380 to 9460* *Exclude 9412 and 9413*	9440/3, 9441/3, 9442/3	Glioblastomas + 9380/3, 9381/3, 9382/3, 9385/3, 9390/3, 9392/3, 9401/3, 9451/3, 9460/3
ICD-O-3.0	*9380 to 9460* *Exclude 9412 and 9413*	9440/3, 9441/3, 9442/3	Glioblastomas + 9380/3, 9381/3, 9382/3, 9390/3, 9392/3, 9401/3, 9451/3, 9460/3
ICD-O-2	*9380 - 9460 and 9481* *Exclude 9412 and 9413*	9440/3, 9441/3, 9442/3, 9481/3	Glioblastomas + 9380/3, 9381/3, 9382/3, 9390/3, 9392/3, 9401/3, 9451/3, 9460/3
PAD (and ICD-7)	ICD7: 193.0 + PAD: 475 476 481 485 486	*NA*	*476, 486*

Notes:

PAD: classification system WHO/C24 Pathological Anatomical Diagnoses. All gliomas are defined by the heading Glioma in the ICD-O-classifications (morphological codes 938-948 ICD-O classification), excluding medulloblastomas (codes 947-9480) and neuronal and mixed neuronal glial tumours (usually out of the group 938-948, except for 9412 and 9413); occurring in the brain (i.e. topographical code C71 of the ICD-O all codes starting with C71, so C71.0, C71.1, C71.2, C71.3, C71.4, C71.5, C71.6, C71.7, C71.8, C71.9). 9421 is the code for pilocytic astrocytoma. In WHO classification ICD-O-3 the morphological code of this tumour is 9421/1, but in the USA, and in the ICD-O-2 this tumour entity has been reported as 9421/3. Therefore both codes have been included, although one of them may not apply. Several new codes were introduced in the new version, ICD-O-3.2, which is recommended for use from 2020 (included in the list because they might be already in use in the registries): 9445 is a new code for GBM IDH mutant, 9385 is a new code for diffuse midline glioma, H3 K27M mutant, 9396 is a new code to represent Ependymoma-RELA fusion positive.