Review Article

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A critical analysis of the MOBI-Kids study of wireless phone use in childhood and adolescence and brain tumor risk

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Abstract: The MOBI-Kids case-control study on wireless phone use and brain tumor risk in childhood and adolescence included the age group 10–24 years diagnosed between 2010 and 2015. Overall no increased risk was found although for brain tumors in the temporal region an increased risk was found in the age groups 10–14 and 20–24 years. Most odds ratios (ORs) in MOBI-Kids were <1.0, some statistically significant, suggestive of a preventive effect from RF radiation; however, this is in contrast to current knowledge about radiofrequency (RF) carcinogenesis. The MOBI-Kids results are not biologically plausible and indicate that the study was flawed due to methodological problems. For example, not all brain tumor cases were included since central localization was excluded. Instead, all brain tumor cases should have been included regardless of histopathology and anatomical localization. Only surgical controls with appendicitis were used instead of population-based controls from the same geographical area as for the cases. In fact, increased incidence of appendicitis has been postulated to be associated with RF radiation which makes selection of control group in MOBI-Kids questionable. Start of wireless phone use up to 10 years before diagnosis was in some analyses included in the unexposed group. Thus, any important results demonstrating late carcinogenesis, a promoter effect, have been omitted from analysis and may underestimate true risks. Linear trend was in some analyses statistically significant in the calculation of RF-specific energy and extremely low frequency (ELF)-induced current in the center of gravity of the tumor. Additional case-case analysis should have been performed. The data from this study should be reanalyzed using unconditional regression analysis adjusted for potential confounding factors to increase statistical power. Then all responding cases and controls could be included in the analyses. In sum, we believe the results as reported in this paper seem uninterpretable and should be dismissed.

Keywords: brain tumors; radiofrequency radiation.

Introduction

The results from the MOBI-Kids study of wireless phone use and brain tumor risk in childhood and adolescence have been published [1]. Cases were aged 10–24 years and diagnosed between 2010 and 2015. The study included 899 cases (response rate 72%) with brain tumors and 1,910 controls operated for appendicitis (response rate 54%). Most cases were diagnosed with neuroepithelial tumor (n=671), mainly glioma (n=556).

The authors' interpretation of the results does not seem justified and is not in agreement with current knowledge of cancer causation from radiofrequency (RF) radiation [2–12]. In fact, most odds ratios (ORs) reported in MOBI-Kids are <1.0, some statistically significant erroneously suggestive of a protective effect for childhood brain tumors. In fact, no OR>1.0, evidence of increased brain tumor risk, was statistically significant.

The paper included six tables of results with risk estimates summarized in Table 1. Of the 254 ORs reported in MOBI-Kids [1], 199 (78%) indicated decreased tumor risk (OR<1.0), whereas 53 (21%) indicated increased risk (OR>1.0), and two ORs were 1.0. Of the decreased risks, 20 ORs were statistically significant. The question is whether these results are scientifically probable. Based upon other epidemiological and mechanistic studies, we believe these results suggest that the MOBI-Kids study is methodologically flawed.

Conducting a multinational, epidemiologic study involving more than 50 scientists with data collected in 14 nations is a complex endeavor with a substantial risk of

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Table 1: Number of odd ratios (OR) reported in Tables 3–8 of the MOBI-Kids study [1].

	Table 3	Table 4	Table 5	Table 6	Table 7	Table 8
OR>1.0	9	9	7	8	9	11
OR=1.0	0	0	2	0	0	0
OR<1.0	39[a]	22	26	44	55[b]	13[c]

[a]6 statistically significant (p<0.05). [b]12 statistically significant (p<0.05); 1 borderline statistically significant. [c]2 statistically significant (p<0.05).

failure. Although the investigators made an effort to salvage the study via sub-studies and post-hoc analyses, we believe they were unsuccessful in overcoming serious methodologic problems. Hence, in our opinion, the results as reported in this paper seem uninterpretable and should be dismissed.

One potential explanation for the many brain tumor risk estimates less than one is participation bias (i.e., selection bias). The study had substantially lower participation rates for controls (54%) than cases (72%) which likely biased brain tumor risk estimates downward. Although the investigators conducted a non-participation study to estimate the amount of this bias, this substudy [13] also had serious limitations (i.e., small sample sizes; differential participation rates) and likely underestimated the amount of selection bias in the primary analyses.

The original study design called for recruitment of 2,000 cases [14]. Due to problems with participant recruitment, the study managed to enroll only 898 cases. Moreover, the primary analyses included only the 671 cases with neuroepithelial brain tumors (NBT). Hence, the study had inadequate sensitivity (i.e., statistical power) to detect even a moderate-sized effect, let alone a small effect, from wireless phone use on brain tumor risk.

The authors of the study appear to agree with our assessment because they concluded in the paper's abstract: "*Further analyses suggest that the large number of ORs below one in this study is unlikely to represent an unknown causal preventive effect of Mobile phone exposure: they can be at least partially explained by differential recall by proxies and prodromal symptoms affecting phone use before diagnosis of the cases. We cannot rule out, however, residual confounding from sources we did not measure. Overall, our study provides no evidence of a causal association between wireless phone use and brain tumors in young people. However, the sources of bias summarized above prevent us from ruling out a small increased risk.*"

Brain tumor incidence

The MOBI-Kids paper cited several studies based on older brain tumor incidence data [15, 16] indicating no increasing brain tumor incidence, e.g. [15] only reported incidence data until 2003.

However, the MOBI-Kids paper failed to cite e.g., a more recent Swedish study which found a statistically significant increase in brain tumor incidence in men and women from 1998 to 2015. The Average Annual Percentage Change (AAPC) increase was seen also in the youngest age groups [17].

A Canadian study on the incidence of primary brain tumors [18] concluded that "*In the adult and older adult groups, incidence, prevalence and age-standardized corrections all increased significantly over the study period [1992–2017], with the age-standardized incidence among adults increasing at 1.3 APC [annual percent change] and that among older adults increasing at 2.0 APC.*" For paediatric brain tumors, APC increased +0.34 for the study period 1992–2017. During 2006–2012, the incidence increased statistically significant (APC +3.26), whereas a decline was seen during 2013–2015 that seems to be caused by an outlier in 2015. Furthermore, it is unclear why the years 2016 and 2017 were excluded from that particular analysis. This study was in MOBI-Kids evaluated to show no increased risk: *"In Canada, no increase in paediatric brain tumors has been observed between 1992 and 2017."*

"Further analyses and comparisons across countries and age groups suggest these may reflect improved data collection practices in surveillance systems, in particular at older ages, making any inference about possible effects of mobile phones difficult." That statement in MOBI-Kids was exemplified by, for example, an Australian study on brain cancer between 1982 and 2012, and mobile phone usage data from 1987 to 2012 [19]. However, that study has been criticized to be biased [20]: "*There are some serious errors in Chapman* et al. [1] *on mobile phone use and brain cancer that warrant the paper's retraction. The authors did not reveal that the Australian cancer data used were only estimates for 2011 and 2012 due to unavailability of data from the state of New South Wales and the Australian Capital Territory (33.8% of Australia's population in 2012).*" Thus, without a reasonable lag time between use of mobile phones and brain cancer incidence, at most 3 years (1987 until 2010) the study is of limited value and should not be cited as no evidence for increasing brain tumor incidence.

Cohort studies

The UK study [21] and the Danish cohort study [22, 23] on mobile phone use were reported by MOBI-Kids to show no increased risk for brain tumors without a thorough review, "*Analyses of large-scale cohort studies (Benson* et al. *2013; Frei* et al. *2011) have not shown an association between mobile phone use and BT [brain tumor] risk*." The studies were cited as no evidence of increased risk, although the paper admitted that these studies were "*subject to substantial exposure misclassification*." In fact, the International Agency for Research on Cancer (IARC) evaluation of tumor risk from RF radiation regarded this Danish cohort study [22, 23] to be uninformative due to serious methodological flaws including lack of information on actual mobile phone use: "*Because of the reliance on subscription to a mobile-phone provider as a surrogate for mobile-phone use, this study involved considerable misclassification in exposure assessment*" and "*showed no increase in risk of relevant tumors, but it lacked information on level of mobile-phone use and there were several potential sources of misclassification of exposure*" [3]. All publications from the Danish cohort have similar deficiencies. A peer-reviewed article concluded that "*After reviewing the four publications on the Danish cohort study, one might rightly wonder whether this cohort was initially set up to show no increased risk* [24]."

The UK cohort study [21] of 791,710 women in the Million Women Study was started between 1996 and 2001. Data on mobile phone use was collected at one time between 1999 and 2005, without questions separating heavy users from light users. Mobile phone use was based on answers to a few questions posed at the time when the women were recruited for the study: "*About how often do you use a mobile phone?", "Never, less than once a day, or every day?"* Those who reported mobile phone use were also asked "*for how long*?" Due to limitations in the study design, including no comprehensive assessment of lifetime mobile phone use, the study is uninformative and should not be used as evidence of lack of cancer risk.

Case-control studies

According to MOBI-Kids:

> "*Up to now, collection of detailed mobile phone history has only been possible in case-control studies. Though they are subject to limitations such as recall bias, large-scale case-control studies in the last decade have suggested a possible association between mobile phone use (and RF energy absorption in the brain) and risk of brain and Central Nervous System (CNS) tumors. These findings are the basis for the IARC Monographs RF evaluation (Baan* et al. *2011)* [2]."

> *"The lack of an increased risk in our study are [is] consistent with those of the CEFALO study of BTs in children and adolescents (Aydin et al. 2011)* [25] *which included a smaller number of cases, diagnosed between 2004 and 2008, with substantially less phone use. They are also consistent with the overall INTERPHONE study* [26] *results which found no overall increase in risk in relation to the level of mobile phone use. Unlike INTERPHONE, we found no increased risk in the highest dose group and no RF dose-related increased risk in the longest-term users."*

These statements are in fact not consistent with what the cited studies found. The Hardell group has published results on brain tumor risk associated with wireless phone use since the late 1990's [27]; for more discussion see [4]. Results for the whole study period were published in 2015 [28]. In addition, the 13 nation Interphone study [26] and the French study [29] provide results for the following meta-analysis.

A random effects model was used for meta-analyses of published studies on glioma, based on a test for heterogeneity. Only the Hardell group also assessed use of cordless phones. Results for highest cumulative use in hours of mobile phones is given from the three available studies with such results [26, 28, 29]. The meta-analysis yielded an odds ratio (OR)=1.90 (95% confidence interval [CI]=1.31–2.76). For ipsilateral mobile phone use the risk increased further to an OR=2.54 (95% CI=1.83–3.52) in the meta-analysis based on 247 exposed cases and 202 controls. For further discussion see [30].

Main results of interest in MOBI-Kids

The temporal lobe is the area of the brain with highest exposure to RF radiation when the handheld phone is used. Table 5 in the MOBI-Kids article is of interest in that context. Ten-plus years since start of wireless phone use yielded an overall OR=1.52 (95% CI=0.43–5.38, <1 year as reference category).

In the age group 10–14 years, for regular use 1+ years before diagnosis OR=1.66 (95% CI=0.43–6.48) was obtained for temporal tumor. In that age group, latency of 5+ years yielded higher risk, OR=2.90 (95% CI=0.62–13.44; <1 year as reference). Thus, the risk increased with increased latency.

In the age group 15–19 years, no increased risk was found for temporal tumor, OR=0.78 (95% CI=0.10–6.05)

for regular wireless phone used 10+ years before diagnosis compared with less than 10 years. The corresponding result for frontal or parietal tumor was OR=2.75 (95% CI=0.33–22.55).

In the age group 20–24 years regular phone used for 10+ years yielded OR=4.16 (95% CI=0.61–28.24) as compared with less than 10 years. For high-grade glioma (the most malignant type), OR=1.32 (95% CI=0.67–2.58) in the 10+ years latency group with <10 years as the reference category was found (Table 6 in article) in that age group.

In Table 5 in the article no calculations of the risk for cumulative use in hours of wireless phone use and laterality of phone use were presented. In carcinogenesis latency (tumor induction time), cumulative wireless phone use and tumor localization in relation to RF radiation exposure are of importance. Furthermore, regular wireless phone users <10 years before diagnosis were used as the reference group (OR=1.0) in the age groups 15–19 and 20–24 years. This group consisted of three cases and three controls in the age group 15–19 years, and five cases and 24 controls in the age group 20–24 years. There is no information if these cases and controls in fact had used wireless phones, but were in these calculations classified as 'unexposed'.

Note that several calculations yielded wide confidence intervals due to low numbers in the reference group. A summary of some methodological issues is given at the end of this article.

There are studies that indicate a promotor effect with short latency for RF radiation [25, 28]. The group with <10 years latency included in the 'unexposed' group in MOBI-Kids may in fact include exposed cases. It is not likely a true unexposed group. Thus, cases with shorter latency than 10 years might have had a brain tumor associated with wireless phone use, but these were included in the unexposed group. This would bias an increased risk towards unity. Many calculations in Table 5 in the study, for example, are based on low numbers with wide confidence intervals. Thus, several strata included less than 10 cases or controls. Since these calculations were based on small samples they have limited possibility to evaluate increased risk.

The results are, anyhow, of interest considering their potential biological relevance. For a null result the ORs would be centered on 1.0. However 78% of the ORs are <1.0, see included ~~Table 1~~, indicating that the results are skewed due to uncontrolled bias and confounding. In fact, adjustment for the overall decreased risks would give even higher ORs for tumors in the temporal region. The risk decreased with increasing time since start of wireless phone use for tumors in the cerebellum and the category "others," see Table 5 in the article. That is not biologically plausible based on current knowledge of RF radiation carcinogenesis.

Table 7 in the article provides results for tumor risk related to cumulative RF-specific energy and extremely low frequency (ELF) induced current density in the center of gravity of the tumor overall and by age group using age-specific quintiles. All analyses of linear trend indicated an effect of both RF and ELF among the cases. This was overall statistically significant for ELF at the center of gravity (linear trend test, p=0.03). In the age group 20–24 years both RF and ELF yielded statistically significant linear trends (p=0.04 and 0.03, respectively). These results are of importance since only the case group was examined thus excluding bias in the assessment of exposure among the controls. It is unlikely that tumor localization influenced recall bias among the cases. The highest exposure is in the tumor indicating an increased risk for both RF and ELF.

ORs and CIs were calculated on cumulative RF-specific energy and ELF-induced current density in the center of gravity of the tumor in Table 7 in the study. It is assumed that the matched control was assigned the same tumor localization as the respective case. Using the controls in these analyses, as expected based on overall results in the study, almost all ORs were below unity indicating a preventive effect. This is in contrast to the results in the case group only, and is another example of the biased assessment of exposure in the control group.

The results should be supplemented with case-case analyses of the tumor dose of RF radiation, similar to Table 5 in [31]. The center within the most exposed area was analyzed in that study with the center outside the most exposed area used as a control and never regular users was the reference category. In the 10+ latency time, a statistically significant risk (OR=2.80, 95% CI=1.13–6.94) was obtained for brain tumor risk.

MOBI-Kids concluded that:

> *"The absence of a positive association between NBT [neuroepithelial brain tumors] risk and levels of RF CSE [cumulative specific energy] and ELF CICD [cumulative induced current density] strengthens our finding of no apparent increased risk of NBT with use of wireless phones (both mobile and cordless)."*

However, this does not correspond to what the study found according to the linear trend tests of estimated RF and ELF tumor dose.

In a case-control study on extremely low frequency (ELF) exposure, an increased risk for glioma was found in the 1–14 years' time window. The authors concluded: "*An increased risk in late stage (promotion/progression) of*

astrocytoma grade IV for occupational ELF-EMF exposure was found." These results showed a late carcinogenesis effect (short latency period) for ELF-EMF [32]. Furthermore, in the Interphone study glioma was associated with occupational ELF-EMF exposure in recent time windows [33]. No doubt these studies should have been cited in the MOBI-Kids paper adding to the evidence of a tumor promotion effect from ELF-EMF. Thus, it is not appropriate to disregard exposure <10 years before diagnosis and include exposed subjects in the unexposed group. Regarding RF radiation it should be noted that the results in the glioma study by Hardell and Carlberg [28] showed that:

> *"The results for latency and ipsilateral mobile phone use (Figure 3) show that there was a higher OR with short latency, and after some decline was seen to give an increasing risk with longer latency (non-linearity, p=0.01). This findings is different from the result for contralateral mobile phone use, see Figure 4 (non-linearity, p=0.74). The results were similar for cordless phone use, data not in figures (ipsilateral, non-linearity, p=0.04, contralateral, non-linearity, p=0.26)."*

> *"For ipsilateral mobile phone use and latency, the curve was slightly different compared with total wireless phone use, with an increased risk for short latency (<10 years), which dropped off slightly before increasing again with longer latency >20 years (non-linearity p=0.01).This finding differs from contralateral mobile phone use (compare Figures 3 and 4). It should be noted that contralateral use was defined as less than 50% of the time. Similar results were found for cordless phone use. These results indicate an early effect in brain tumourigenicity (initiation) and a late effect (promotion), as discussed elsewhere* [24]."

In Appendix 2 of the Interphone study [26], the analysis of mobile phone use was restricted to ever regular users and the latency period of 1–1.9 years was used as the reference category. An increased risk for glioma was found since start of regular mobile phone use (2–4 years: OR=1.68, 95% CI=1.16–2.41; 5–9 years: OR=1.54, 95% CI=1.06–2.22) with the highest risk in the 10+ years category (OR=2.18, 95% CI=1.43–3.31) [26].

Furthermore, in the only previous study on mobile phone use and brain tumor risk in childhood, the CEFALO study, several risk estimates increased with short latency [25]. Compared with never regular use, brain tumor risk estimates increased with the amount of time since first ipsilateral mobile phone use (≤3.3 years: OR=1.73, 95% CI=0.87–3.44; 3.3–5.0 years: OR=1.53, 95% CI=0.62–3.76; >5.0 years: OR=3.74, 95% CI=2.75, 95% CI=0.93–8.06).

In CEFALO [25], analysis based on operator-recorded use found that risk estimates increased with the amount of time since first mobile phone subscription (1.8–2.8 years: OR=1.71, 95% CI=0.85–3.44; >2.8 years: OR=2.15, 95% CI=1.07–4.29) with a statistically significant trend (p=0.001). It should be noted that for tumors in the temporal or frontal lobes or cerebellum the OR was 1.0 (95% CI = 0.58–1.72) whereas statistically significant increased risk was obtained for other localizations in the brain (OR=1.92, 95% CI=1.07–3.44). By tumor morphology, astrocytoma and other glioma yielded OR=1.14 (95% CI=0.66–1.97), whereas for other types of tumors the OR was 1.65 (95% CI=0.93–2.93).

Methodological issues

Based on scientific evidence it was inappropriate for MOBI-Kids to exclude certain types of brain tumors, to exclude tumors originating in the middle of the brain, and to consider short latency as no exposure. Brain tumor morphology and anatomical localization in childhood is different from adults (see discussion below). Excluding exposure with short latency prec[illegible]s the possibility to find a risk-promoting effect from RF radiation and would bias an increased risk for long time latency towards no effect due to including exposed cases with short latency in the unexposed group. All of these scientific analytical method errors bias the study from finding a true increased risk.

Confounding

One possible confounding factor may be proxy replies to the questions. The authors noted that:

> "*The decreasing trend [OR] was mainly seen in the 15–19 years old age group. This age-group is characterised by a mixed profile of respondents, with substantially more cases than controls with proxy only respondents…. Analyses restricted to interviews with the subject him/herself alone or with a parent gave ORs that were generally closer to one, suggesting that information on wireless phone history collected from parents (who may be unaware of their children's true) alone may not be reliable. These observations suggest that at least part of the reduced ORs may be related to proxy interviews bias*."

In general, parents might have felt "guilty" for the child's brain tumor and thus under-estimated exposure. This could explain the results especially in the 15–19 years age group. Moreover, since parents were present during the interviews, adolescents with brain tumors may have under-reported their mobile phone use due to concerns that their parents would restrict their mobile phone use, e.g., [34]. Recruitment of cases for this 14-country study was unbalanced varying from 16 cases in New Zealand to 208 cases in

Spain. The majority of cases came from three countries: Spain, Italy, and France. In contrast, in CEFALO most cases were from three Nordic countries (not included in MOBI-Kids).

Although some sensitivity analyses were reported to maximize statistical power, the authors should conduct unconditional logistic regression analyses with stepwise addition of potential confounding factors (e.g. gender, age, year of diagnosis, country, proxy, proxy/index, or index only interview, time between diagnosis and interview, and parental education).

Laterality

The authors disregarded what is known about absorbed cell phone radiation in children, e.g., [35–37].

> "*To maximise the statistical power to detect a risk related to RF dose if it exists, tumors originating in the middle of the brain, where little RF energy deposition from wireless phones is expected (Cardis* et al. *2008), were excluded.*"….

> *"Because absorption of RF energy from mobile phones is highly localized (Cardis et al. 2008; Lee et al. 2019, 2017; Wiart 2016; Wiart et al. 2008),* [38–42] *analyses of wireless phone use variables were also conducted according to the anatomical location of the tumour: temporal lobe, frontal or parietal lobes, cerebellum, and others (occipital and middle brain structures)."*

The results from ipsilateral and contralateral use of the wireless phone should have been presented. Such data seem to exist since the results in Tables 7 and 8 in the paper appear to be based on tumor-specific RF energy.

Due to the smaller head, thinner skull bone and higher tissue conductivity, a larger part of the brain is exposed in childhood compared to adults. Furthermore, the developing brain would be more sensitive to toxins compared with adults. Thus, midline tumors as well as infratentorial tumors are of importance to investigate. It is unknown which tumors in the brain of a child are at risk from mobile phone use, and consequently there is no scientific basis to *a priori* exclude some brain tumors as the authors have done. There may also be different sensitivity to RF radiation in different structures of the brain tissue, a fact disregarded in MOBI-Kids. The exposure to the child's brain is substantially higher, up to 2–3 times greater than in adults [36, 37].

The brain of a human is a highly complicated biological system, and the influence on different parts of the brain and skull from RF radiation and EMF in children is unknown. Animal studies have shown that there are windows where less radiation intensity is more harmful than more intensive levels; thus, one cannot conclude that less exposed parts of the brain are not at risk [43].

Type of tumor and anatomical localization

The reason to exclude middle brain tumors is not scientifically justified. All brain tumors regardless of histopathology and localization should have been included. It is noted that '*tumors originating in the middle of the brain*' were excluded. This is in contrast to next statement that analyses were conducted for tumors in "*cerebellum, and others (occipital and middle brain structures).*" That statement makes us question the methodologic choices made by the authors and raises concerns regarding selection bias.

Most medulloblastoma are primarily midline neuroepithelial cerebellar tumors with about 75% that arise in vermis (midline) with projection into the fourth ventricle. The majority of cases occur up to the age of 19 years; in fact, 70% occur in children under the age of 16. Although most cases occur in the age group 0–9 years, a substantial number is found in the age group 10–19 years, i.e. the age group included in MOBI-Kids. No data are presented for medulloblastoma, According to Supplement Table S1 on morphology, medulloblastoma was included in MOBI-Kids [1]. It is unclear what was studied which leaves the possibility for study center variability. Since medulloblastoma is prevalent in childhood, these tumors should have been reported.

The study initiated recruitment of cases in 2010; yet, the stated reason for excluding some tumors is mostly based on studies published after the initiation of recruitment. There is no evidence that any part of the brain is unexposed to RF radiation when the hand-held wireless phone is used. Thus, including all cases would increase the likelihood of detecting a dose-response effect.

The study on clinical presentation of the MOBI-Kids study does not summarize all of the data [44]. A table with all tumors based on type and anatomical localizations should be included, also showing those excluded from the study. At the time of the study an increased risk for both glioma and acoustic neuroma was known, e.g. see the IARC 2011 evaluation [2, 3]. Further studies indicate that RF radiation can be multi-carcinogenic with promotion/induction of tumors at multiple sites with different histopathology [5–8].

Ependymoma was included according to the morphology codes in Table S1. This is primarily a central tumor, which represents 6–12% of intracranial tumors in children [45]. It is most common in the 4th ventricle and the spinal cord (not part of the study), followed by the lateral ventricles and

the 3rd ventricle. Thus, a central tumor would be included according to morphology but should be excluded due to the study protocol (central tumor). Ependymoma should have been discussed, and results presented. Clarification is needed.

Craniopharyngioma represents 5–10% of childhood intracranial tumors [45] and was excluded according to the morphology codes. It is a central tumor in the suprasellar region. Although it is a rare tumor, it should have been included and discussed due to its prevalence.

Some studies indicate an association between pituitary tumors, a central brain tumor, and RF radiation. In fact, the National Toxicology Program (NTP) animal study showed an indication of increased incidence of pituitary tumors. An increasing incidence of pituitary tumors since the 1990s was reported in Sweden; see figure in [8]. A sharp increasing incidence was also found in the USA during 2013–2017 in the age group 10–19 years, see Figure 11 in [46].

According to the Swedish Cancer Register, the annual percent change (APC) in age-standardized pituitary tumor incidence in the age group 10–24 years during 1980–2020 increased in males 5.58% (95% CI=3.98, 7.21%), and in females 6.83% (95% CI=4.32, 9.40%) (http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer).

It is unclear if MOBI-Kids included these tumors. Certainly, pituitary tumors are most interesting in relation to studies indicating an association with RF radiation. Not discussing pituitary tumors or not including them in the study is a major deficit in MOBI-Kids.

According to the study methods, pinealoma (pineocytoma), a central brain tumor, was excluded. It affects all ages including childhood. It is not clinically justifiable to exclude this tumor type.

Acoustic neuroma (schwannoma) would have been of interest to discuss considering the association with exposure to RF radiation [3, 47]. The increased risk in epidemiological studies is supported by animal studies [5–8]. According to the morphology code, it was included in the study, however without any presentation of results. Few cases would be expected based on the incidence in the age range in the study [45].

A study on mice carrying a lymphomagenic oncogene exposed to RF radiation showed a statistically significant increased risk for malignant lymphoma [48]. A case report on brain lymphoma in a person with long-time mobile phone use with most exposure in the tumor area is of interest [49]. In female mice exposed to RF radiation an increased incidence of lymphoma was found [5, 8]. Given the substantial effort to study brain tumors in MOBI-Kids, brain lymphoma should have been included and reported in spite of expected low numbers.

The study also excluded central tumors in the fourth ventricle. Another issue is brain stem tumors which were not discussed in the MOBI-Kids paper. The anatomical distribution for brain tumors in children differs from adults with more centrally-located tumors [50].

All brain tumors were not analyzed as a group since different risk factors were assumed to exist based on tumor type. There is no scientific justification for this except for some embryonal and rare genetic tumors. Furthermore, also with that assumption all brain tumors should have been included. Thus, the main analysis should have included all cases followed by subgroup analyses. This is also supported by the NTP study findings with increased incidence of several tmour types. Some animal studies indicate a promoter/co-carcinogenic effect from RF radiation [51, 52]. The failure to include all tumor types in the main analysis is not supported by the literature, A summary of all diagnosed brain tumors during the study period 2010–2015, regardless of tumor type and anatomical localization, should have been included. This should include all identified brain tumors, all included in the study, and finally, all that participated. Thus, histopathology and anatomical tumor localization should be given for all cases in these three groups. Thereby a clearer picture would have been provided regarding what was done and what was not done in the study. Numbers of expected cases could have been provided based on person-years at risk in the included study population.

Controls

"*Controls were individually matched to cases on sex, age (±1 year for cases below 17 years and ±2 years for cases aged 17 and over), date of interview (±1 year) and region (large geographical areas within countries).*"

The methods are not well described, e.g. matched on age ±2 years in the older group (17+ years) in contrast to ±1 year in the younger groups. There seems to have been a pool of controls used for *post hoc* matching which might create selection bias.

According to Table 1 in the paper, one control could be used for several cases. This includes repeated use of controls: the same control could be matched to more than one case.

"*Though the study protocol required that two matched controls be selected for each case, it was not always possible to identify controls fulfilling the matching criteria. To minimize the number of cases without controls, and ensure that matching was as close as possible, post-hoc matching was performed, drawing from the pool of all controls recruited for the study.*"

"*The three most closely matched controls were selected for each case (where there were more than three eligible controls) and controls could be matched to more than one case (repeat sampling). Ninety nine percent (99%) of cases were matched*."

The procedure with *post hoc* matching and different numbers of controls depending on where it is presented in the paper seems to make the study results less reliable. The results are based on 899 responding cases and 1,910 controls, thus more than the double.

Only surgical controls operated for appendicitis were used. Population-based controls could have been used as an additional group as well as patients diagnosed with other diseases except cancer. In fact, it has been postulated that microwave radiation can increase the incidence of appendicitis. Research on health effects called microwave sickness was reported in 1998, page 314 [53]:

> "*It's [Microwave sickness] first signs are low blood pressure and slow pulse. The later and most common manifestations are chronic excitation of the sympathetic nervous system [stress syndrome] and high blood pressure. This phase also often includes headache, dizziness, eye pain, sleeplessness, irritability, anxiety, stomach pain, nervous tension, inability to concentrate, hair loss, plus an increased incidence of appendicitis, cataracts, reproductive problems, and cancer. The chronic symptoms are eventually succeeded by crisis of adrenal exhaustion and ischemic heart disease [the blockage of coronary arteries and heart attacks]*."

An increasing incidence of colorectal cancer in birth cohorts under the age of 40 has been suggested to be associated with RF radiation from mobile phones [54]. Also the incidence of appendicitis seems to be increasing "*…the incidence is increasing. The peak incidence is in the 15-19-year group*" [55]. It should be noted that RF radiation may have an effect on inflammation [56]. Exposure from 900 MHz mobile phone RF radiation lead to epigenetic detrimental changes in ERα promotion methylation pattern in colon cells in a rat study [57].

Obviously appendicitis might be associated with microwave (RF radiation) exposure. Thus, using patients with appendicitis as the reference group, and as the only one, would bias the results towards null, or even explain the generally decreased ORs. Although the association between appendicitis and RF radiation is not firmly established the selection of control group in MOBI-Kids is questionable.

Interviews

Assessment of exposure was not performed blinded as to case or control status. That potential for observational bias should be analyzed and discussed in more detail, as well as the potential to underestimate exposure in cases or their parents due to knowledge of the general discussion that RF radiation might cause brain tumors. The same stressful situation would not apply to the controls.

It must be noted that the clinical pattern in childhood brain tumor cases differs from adults. This is based largely on increased intracranial pressure since most tumors are in the posterior fossa and midline structures. These tumors lead to early obstruction of the cerebro-spinal fluid circulation increasing the pressure, especially for midline tumors. It must also be stressed that mid-line tumors seem to have been excluded from MOBI-Kids according to the described methods, a scientifically unjustified method.

Assessment of exposure

> *"If data on the age at start or stop of wireless phone or number or duration of calls were missing, these were imputed based on the average of each variable among the participants in the same country, sex and age."*

Thus, since one control was used for several cases, bias in assessment of exposure among controls would have a large impact on the results. Furthermore, using "*average for each variable"* is not the actual exposure of each participant.

> *"For periods when a subject reported using hands-free devices or the speaker of their mobile or cordless phone, the amount of use was reduced by 18.5, 7 or 3.5%, depending on whether the devices were used half the time or more, less than half the time, or never or rarely. These values were determined from the results of the MOBI-Expo validation study (Goedhart et al. 2018)* [58]. *Similarly, if hands-free use was through a Bluetooth device, the reduction factors were 10, 1 and 0% respectively."*

These percentages seem incorrect. For example, an 18.5% reduction for a person using a hands-free device "half the time or more" is a small reduction factor which could enhance exposure misclassification. This represents a major problem in the study.

No results were presented for ipsilateral or contralateral exposure. However, tumor localization was used in the analysis of RF dose estimates in Table 7 in the article. It seems as if the actual side for each person was not used but instead analysis was conducted with proxy reports. It is unclear why these data on assumed anatomical tumor localization were not used for laterality analysis: ipsilateral and contralateral RF radiation exposure.

Note also that the validation study did not include any cases, but instead employed an external study group and perhaps some controls. Furthermore, it seems as if these results were derived from a study on volunteers who did

not participate in MOBI-Kids, designed by Whist Lab, Paris, and a Telecom Institute.

> *"…laterality of phone use was attributed as follows, based on the results of the validation study: 70% and 30%, respectively, on the right and left side, for subjects who reported use mainly on the right side of the head; 50% and 50% for those who reported use predominantly on the left; and 60% and 40% for subjects who reported using the phone on both sides of the head."*

Thus, this procedure does not seem to have been based on exposure reported by the study subjects. Laterality of phone use seems to have been based on a proxy assumption derived from another study and not assessed for each individual person in the study. If so, the section on RF dose analysis would be biased. There is no scientific justification for this method. No cases were included in the validation study. Thus, if there is an increased brain tumor risk for ipsilateral exposure, as shown in other studies and is of biological relevance, such exposure would be reduced for the exposed case. Previous epidemiological studies have shown increased risk for brain tumor associated with ipsilateral exposure, e.g. [28, 30]. Thus, if an association exists more cases than controls would be expected to have ipsilateral exposure. However, in MOBI-Kids regarding laterality, exposure was reduced with 30% for right side and with 50% for left side. Equal use of both sides should be 50%. This method introduced exposure misclassification which would underestimate the risk and constitutes a bias in the study.

Vested interests

The paper describing the protocol for the MOBI-Kids study [14] indicated that four authors had conflicts of interest during study design and data collection: Krewski, Sim, Taki, and Wiart; yet, the initial version of the latest MOBI-Kids paper [1] declared no competing interests. This oversight was partially corrected by amending the current version of paper to designate "competing interests" for Krewski, Wiart, Kundi, and Momoli. We do not understand why Sim and Taki were excluded from the current list because these two authors had conflicts of interest during the design and data collection period.

Wiart was employed from 1997 to 2015 by Orange/France Telecom and was during 2009–2015 head of Whist Lab Paris funded by Orange. Orange/France Telecom is a telecommunications company with obvious economic interests in the outcome of MOBI-Kids [42]. This lab developed the exposure measurement tools for the study, another potential conflict of interest [58].

France Telecom was from the start part of the MOBI-Kids consortium, as shown by project leader Elisabeth Cardis in a presentation of the research project [59]. Obviously J Wiart was employed by France Telecom/Orange during the planning, design and performance of the study. He was one of the principal investigators on dosimetry in the study concluding that "*To maximize the statistical power to detect a risk related to RF dose if it exists, tumors originating in the middle of the brain, where little RF energy deposition from wireless phones is expected (Cardis* et al. *2008), were excluded.*" Joe Wiart from France Telecom was coauthor of the study referred to as the basis for this exclusion.

Further "*… absorption of RF energy from mobile phones is highly localized (Cardis* et al. *2008; Lee* et al. *2019, 2017; Wiart 2016; Wiart* et al. *2008),.*" [38–42]. This statement is not quite correct and is not in agreement with other studies on dosimetry on the child's brain. The statistical power would certainly increase by including all brain tumors regardless of anatomical localization. Furthermore including central tumors such as pituitary tumors in the sella would increase the possibility to analyze exposure gradients, i.e. ipsilateral, central and contralateral tumor localization. Of concern is also that tumors of interest were thereby excluded from the study, not only based on anatomical localization but also specific types, e.g. pituitary tumors. In 2010 a study concluded that "*The exposure of regions inside the brains of young children (e.g. hippocampus, hypothalamus, etc.) can be higher by more than 2–5 dB in comparison to adults* (Section 3.2). *This should be considered in the design of volunteer studies*" [35]. That fact was not applied in MOBI-Kids.

In addition four other Orange employees, were also involved in the MOBI-Kids study "consortium" mentioned in the study protocol publication 2014: "*Orange – Joe Wiart, E. Conil, N. Varsier, T. Sarrebourse, and Abdelhamid Hadjem*" [14]. Only Joe Wiart appears in the "Conflicts of interest" section; "*J Wiart has no conflict of interest to declare*" [1].

Furthermore, according to the study protocol Ae-Kyoung Lee and H.-D. Choi from Electronics and Telecommunications Research Institute (ETRI), from Korea were also members of the "consortium". Although Ae-Kyoung Lee is a coauthor of the final study, there is no mention of the conflict of interest in terms of being employed by ETRI. This is a Korean national institute which focuses on developing communications and AI technologies. Among its listed achievements is the development of the "*world's first 4-generation mobile communication system LTE-Advanced*." Furthermore on May 8, 2015 "*at Samsung's Seocho office the ETRI signed a Memorandum of Understanding (MOU) with Samsung Electronics to cooperate*

on the Internet of Things (IoT)" (https://www.etri.re.kr/engcon/sub1/sub1_03.etri; https://readwrite.com/open-source-etri-samsung-forge-partnership-for-iot-standards/).

General comments

"*Currently, there is no conclusive biological evidence that RF or ELF at the levels emitted by mobile phones may increase the risk of brain cancer (ICNIRP, 2020; SCENIHR, 2015), hence our results are consistent with the knowledge to date*" [60, 61].

This assertion is false. The MOBI-Kids study is flawed methodologically so that this conclusion cannot be derived from that first statement regarding conclusive proof. It shows nothing useful, and it is not a demonstration of lack of risk for brain tumors from RF radiation. Interestingly, the authors rely both on ICNIRP [60] and SCENIHR [61] in spite of the critique of these studies to be biased [62, 63].

SCENIHR [61] represents old data and has not been updated. ICNIRP [60] does not seem to be based on current knowledge in this area and may have conflicts of interest as discussed in peer-reviewed articles [12, 62, 63].

Results from meta-analyses are not included [30, 64–67]. It is striking that the article lacks reference to the animal studies showing increased cancer risk [51, 52]; and only one of the NTP studies [6], was included in the MOBI-Kids discussion. Also, results on DNA damage are missing although studies show that RF radiation causes both oxidative stress [68], and DNA-damage [69, 70].

The authors need to explain why their results conflict with human epidemiologic studies that found increased risk for brain tumors, animal data and mechanistic studies that altogether indicate an increased risk. The MOBI-Kids study shows consistently decreased risks, i.e., protective effects from RF radiation. Either all studies showing carcinogenic potential are false and MOBI-Kids results are correct or the opposite is true. A thorough discussion is needed

As outlined in our comments several aspects of good epidemiological practice are not covered in the article. Such aspects are presented in [71]: "*Two criteria for an interpretation of non-effect are that the relative risk estimate be near unity and that the confidence interval be narrow; lack of statistical significance has no bearing on this issue.*"

Summary

– In our opinion, the results as reported in the MOBI-Kids paper seem uninterpretable and should be dismissed.
– All brain tumor cases should have been included regardless of histopathology and anatomical localization.
– Only surgical controls with suspected appendicitis were used. Yet, increased incidence of appendicitis has been postulated to be associated with RF radiation.
– Start of wireless phone use up to 10 years before diagnosis was in some analyses included in the unexposed group. This would bias the ORs towards unity.
– The results indicate an increased risk for tumors in the temporal brain region in spite of methodological issues based on low numbers in several categories.
– Linear trend was in some analyses statistically significant in the calculation of RF-specific energy and ELF-induced current in the center of gravity of the tumor. Additional case-case analysis should have been performed.
– The data from this study should be reanalyzed using unconditional regression analysis adjusted for potential confounding factors to increase the statistical power.

Finally, it is unfortunate that after such a major investment of resources that little can be learned at this time from the MOBI-Kids study about the risk of brain tumors from wireless phone use in young people. Since the study addresses an issue critical to public health and the majority of the funding was from the European Commission, the MOBI-Kids data set should be publicly archived making it available to the scientific community to enable the data to be re-analyzed using different assumptions and methods.

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