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COSMOS: A methodologically-flawed cohort study of the health effects from exposure to radiofrequency radiation from mobile phone use

To the Editors, Environment International

We write to point out serious methodological problems with the Cohort Study on Mobile Phones and Health (COSMOS) brain tumor risk paper (Feychting et al., 2024). Because of these flaws, the study does not provide reliable estimates of the risks of tumors associated with exposure to mobile phone radio frequency radiation (RFR). This paper which summarizes interim results from this 25-plus year cohort study (Schüz et al., 2011) demonstrates many of the overall study's shortcomings.

1. Problems with exposure assessment

At baseline, COSMOS collected data on the frequency and duration of mobile phone calls based on self-reports, partially supplemented with data from operator records from telecommunications providers. This is a poor proxy for the amount of RFR exposure from a mobile phone. Misclassification of RFR exposure was substantial because the amount of exposure from a mobile phone varies by up to four orders of magnitude depending on the cellular network technology and the strength of the signal from the cell tower (Wall et al., 2019). COSMOS did not account for this variability. The study also did not control for other sources of RFR exposure, including cordless phones, personal wireless devices, Wi-Fi routers, and cell towers.

The study used mobile phone use data at baseline to predict brain tumor incidence about seven years later (median = 7.12 years). During this time interval the cellular technology, types of mobile phones and patterns of mobile phone usage changed, and the density of cell towers or masts increased. All of these factors would alter the RFR exposure over time and reduce the ability of the baseline data to predict any health outcomes. The multiple sources of random and systematic measurement error discussed above contributed to substantial misclassification of the three comparison groups in terms of RFR exposure and biased the study results, because of its cohort design, towards the null (Setia, 2016).

Since almost everyone in this cohort study regularly used mobile phones at baseline (including two-thirds who used mobile phones for 10 or more years) and many were exposed to others sources of RFR (e.g., cordless DECT phones, cell towers, Wi-Fi), there was no unexposed group. That the authors chose to use the bottom 50 % of the mobile phone use distribution as the reference group instead of a more extreme percentile cutoff (e.g., the bottom decile of mobile phone use) does not seem defensible. Comparing the top quartile or decile of mobile phone use to the bottom 50 % (which averaged up to 10.6 min per day of call time) when there is considerable measurement error as in the present study reduces the likelihood of finding a difference in tumor risk across exposure strata. Thus, this choice of a reference group further biased the results towards the null.

2. Problems with outcome assessment

The incidence of brain tumors may be under-reported in the five national cancer registries that this study relied upon to assess outcomes. For example, in Sweden, Hardell and Carlberg (2015a) found that many brain tumors reported in the national inpatient registry were never reported to the national cancer registry. They concluded, "In summary this study shows that the Swedish Cancer Register is not reliable to be used to dismiss results in epidemiological studies on the use of wireless phones and brain tumour risk and should not be used as reference for such statements.".

Despite the potential under-reporting of brain tumors in cancer registries, the overall glioma incidence rate in the COSMOS study was rather high (8.11 per 100,000) compared to population studies (Bondy et al., 2008). Yet the study group was almost two-thirds (64 %) women who typically have a lower glioma incidence rate than men (Bondy et al., 2008). Thus, considering the misclassification of RFR exposure, individuals in the bottom 50 % of the cumulative mobile phone use distribution may have been at increased risk of glioma.

In contrast to the high incidence of glioma in this study, the incidence rate for meningioma was lower than expected (4.85 per 100,000), especially since women have a higher incidence of meningioma than men and two-thirds of the sample were women. That the incidence of glioma exceeded meningioma in this study suggests that meningioma, the most common primary brain tumor (Bondy et al., 2008), was under-reported to the cancer registries in one or more of the participating countries.

3. Latency, type and location of tumors

Most human cancers have long latencies, requiring many years to decades after exposure to carcinogens before clinical presentation and diagnosis (Armenian, 1987; Nadler and Zurbenko, 2022). Accordingly, it is critical in cohort studies like COSMOS to stratify on the total length of time between initiation of any given level of exposure – in this case to RFR – and the date of cancer diagnosis, especially since so many members of the COSMOS cohort already had many years of substantial RFR exposure when recruited. Unfortunately, this stratified analysis, summarized in Table 4 of the paper, had insufficient number of cases occurring in the all-important long-latency strata of "10–14 years" and especially ">15 years" since first exposure, to be able to rule out (based on the relative risks' 95 % confidence intervals) 28 % elevated risks for glioma after 10 years, or 52 % elevated risks after 15 years of latency. [For meningioma, with even fewer cases ascertained, these 95 % confidence intervals could not exclude relative risks of 4.69 and 2.59 after 10–14 years and > 15 years, respectively.] In contrast, such analyses of

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Swedish glioma associations with RFR exposures have shown clear evidence of such latency-related phenomena (Hardell and Carlberg, 2015b). Furthermore, Hardell and Carlberg were able to show clinically significantly shorter latency periods (average latency of 16 years for an increasing relative risk to reach 2) for gliomas *ipsilateral* to the ear normally used by subjects on their cell phones, compared to *contralateral* tumors (average latency of 28 years for the relative risk to reach 2). This differential latency is highly suggestive of carcinogenesis, based on two of Bradford Hill's classic (Hill, 1965) nine criteria for assessing causation: dose–response relationship and specificity of association (with regard to laterality).

This interim study by Feychting et al. (2024) does not have a sufficient number of subjects followed for more than a decade after RFR exposure began to rule out elevated risks of these two tumors after the most relevant latent periods for carcinogenesis. The appendix in this paper and future follow-up studies should report brain tumor incidence by type and location. For future follow-up studies, prior research (e.g., Hardell et al., 2015b; Schüz et al., 2011; Philips et al., 2018) indicates that COSMOS should report the effects of cumulative exposure to wireless phone use (cordless phones and mobile phones) on glioma and glioblastoma incidence and by the location of tumors, especially in the frontal and temporal lobes, and the risk for ipsilateral versus contralateral tumors. The authors should also compare their annual tumor incidence rates to age-adjusted rates from the cancer registries of the countries participating in the study.

4. Statistical issues

Although the authors acknowledged that "Statistical power was limited for meningioma and acoustic neuroma," we contend that glioma with only 149 incident cases in this study of 1.836 million person years also had limited statistical power. The confidence intervals for the hazard ratios were large. Moreover, the power analysis in the COSMOS design paper (Table 2, Schüz et al., 2011) assumed an annual incidence rate of 15 per 100,000 for brain tumors, whereas the glioma annual incidence rate in the current study was 8.11 per 100,000. Thus, no analysis of tumor risk in this paper had adequate statistical power.

We question whether the study adequately addressed the heterogeneity among countries. The authors reported, "Statistically significant heterogeneity between the UK and the other countries was found in some analyses of meningioma and acoustic neuroma, which may reflect differences in ascertainment for these mostly benign tumours across countries." Furthermore, the cumulative amount of mobile phone use at baseline varied greatly: the upper tertile ranged from 198 h in Netherlands to 1,433 h in Finland (Supplementary table S4). Due to legal constraints, the UK data were analyzed separately and combined through random-effect *meta*-analyses rather than pooled with data from the other four countries.

The Data Availability section of the paper states, "The data that has been used is confidential." If the authors are using this as the reason not to share their data, then the results cannot be confirmed by independent investigators. Since these data have potentially important policy implications, the data set must be accessible to other researchers. De-identification procedures have been developed to protect confidentiality when sharing data (Huser et al., 2018, Institute of Medicine, 2015).

5. Industry research funding

Funding bias is well-recognized in biomedical research (Bekelman et al., 2003). Industry-funded studies were less likely to report statistically significant health-related effects associated with mobile phone use than non-industry funded studies (Huss et al., 2007; Moskowitz et al., 2020). For example, a review of experimental studies concluded, "industry-sponsored studies were least likely to report results suggesting effects… The source of funding and conflicts of interest are important to consider in this area of research (van Nierop et al., 2010).

COSMOS was partially funded by the telecommunications industry in three countries, Finland, Sweden, and the United Kingdom (Feychting et al., 2024). Although the authors reported a "firewall" agreement ensured "complete scientific independence," the study design was negotiated with Ericsson prior to adoption of this agreement (Monica Kleja, NyTeknik, May 30, 2012; https://www.nyteknik.se/nyheter/stralforskare-kringgar-avtalet-om-oberoende/1752342 (accessed 3/25/2024)). In our opinion, institutional support or research funding from industry constitutes an ongoing, competing financial interest because industry can terminate future funding should investigators fail to protect industry interests when they publish their research.

6. Conclusions

Given the serious methodologic problems with this interim COSMOS paper discussed above, we recommend that the authors retract their conclusion: "Our findings to date, together with other available scientific evidence, suggest that mobile phone use is not associated with increased risk of developing these tumours.".

To support this assertion the authors relied on evidence from three cohort studies (Feychting et al., 2024; Schüz et al., 2006; Schüz et al., 2022) with weak methodology (Ahlbom et al., 2007; Birnbaum, 2022; Moskowitz, 2022; Söderqvist et al., 2012). For example, IARC concluded, "reliance on subscription to a mobile phone provider, as a surrogate for mobile phone use, could have resulted in considerable misclassification in exposure assessment" (Baan et al., 2011). Schüz et al. (2022) did not provide data on cumulative phone use. To support their "no association" conclusion, the COSMOS authors also cited time-trend studies; yet, these studies reported significant increases in brain tumor incidence in age-specific subgroups (e.g., de Vocht, 2021; Deltour et al., 2022; Elwood et al., 2022: Ostrom et al., 2022). Finally, the COSMOS authors cited a review of case-control studies that dismissed the results of the cumulative call time analysis by relegating it to the appendix (i.e., Supplemental Figure 2, Röösli et al., 2019).

In contrast to Röösli et al. (2019), Choi et al.'s (2020) systematic review and *meta*-analysis of 46 case-control studies"found significant evidence linking cellular phone use to increased tumor risk, especially among cell phone users with cumulative cell phone use of 1000 or more hours in their lifetime," and called for high quality, prospective cohort studies to confirm the results of the case-control research.

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Joel M. Moskowitz: Conceptualization, Writing – original draft, Writing – review & editing. **John W. Frank:** Writing – review & editing, Writing – original draft. **Ronald L. Melnick:** Writing – original draft, Writing – review & editing. **Lennart Hardell:** Writing – review & editing. **Igor Belyaev:** Writing – review & editing. **Paul Héroux:** Writing – review & editing. **Elizabeth Kelley:** Writing – review & editing. **Henry Lai:** Writing – review & editing. **Don Maisch:** Writing – review & editing. **Erica Mallery-Blythe:** Writing – review & editing. **Alasdair Philips:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [I.B. has served as the plaintiff's expert witness in a case involving radiofrequency radiation. All other authors declare no competing interests.].

Data availability

No data was used for the research described in the article.

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References

Ahlbom A, Feychting M, Cardis E, Elliott P. Re: Cellular telephone use and cancer risk: update of a nationwide Danish cohort study. J Natl Cancer Inst. 2007 Apr 18;99(8): 655; author reply 655-6. 10.1093/jnci/djk143.

Armenian, H.K., 1987. Incubation periods of cancer: old and new. J. Chronic Dis. 40 (Suppl 2), 9S–15S. https://doi.org/10.1016/s0021-9681(87)80004-8.

Baan, R., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Islami, F., Galichet, L., Straif, K., 2011. WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol. 12 (7), 624–626. https://doi.org/10.1016/s1470-2045(11)70147-4.

Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003 Jan 22-29;289(4):454-65. 10.1001/jama.289.4.454.

Birnbaum, L.S., Taylor, H.S., Baldwin, H., Ben-Ishai, P., Davis, D., 2022. RE: Cellular Telephone Use and the Risk of Brain Tumors: Update of the UK Million Women Study. J. Natl Cancer Inst. 114 (11), 1551–1552. https://doi.org/10.1093/jnci/djac110.

Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, Kruchko C, McCarthy BJ, Rajaraman P, Schwartzbaum JA, Sadetzki S, Schlehofer B, Tihan T, Wiemels JL, Wrensch M, Buffler PA; Brain Tumor Epidemiology Consortium. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. Cancer. 2008 Oct 1;113(7 Suppl):1953-68. 10.1002/cncr.23741.

Choi, Y.J., Moskowitz, J.M., Myung, S.K., Lee, Y.R., Hong, Y.C., 2020. Cellular phone use and risk of tumors: systematic review and meta-analysis. Int. J. Environ. Res. Public Health 17 (21), 8079. https://doi.org/10.3390/ijerph17218079.

de Vocht, F., 2021 Dec. Interpretation of time-trends (1996–2017) of the incidence of selected cancers in england in relation to mobile phone use as a possible risk factor. Bioelectromagnetics 42 (8), 609–615. https://doi.org/10.1002/bem.22375.

Deltour, I., Poulsen, A.H., Johansen, C., et al., 2022. Time trends in mobile phone use and glioma incidence among males in the Nordic countries, 1979–2016. Environ. Int. 168 https://doi.org/10.1016/j.envint.2022.107487.

Elwood, J.M., Win, S.S., Aye, P.S., et al., 2022. Trends in brain cancers (glioma) in New Zealand from 1995 to 2020, with reference to mobile phone use. Cancer Epidemiol. 80 https://doi.org/10.1016/j.canep.2022.102234.

Feychting, M., Schüz, J., Toledano, M.B., Vermeulen, R., Auvinen, A., Poulsen, A.H., Deltour, I., Smith, R.B., Heller, J., Kromhout, H., Huss, A., Johansen, C., Tettamanti, G., Paul, E.P., 2024. Mobile phone use and brain tumour risk – COSMOS, a prospective cohort study. Environ. Int. https://doi.org/10.1016/j.envint.2024.108552.

Hardell, L., Carlberg, M., 2015a. Increasing rates of brain tumours in the Swedish national inpatient register and the causes of death register. Int. J. Environ. Res. Public Health 12 (4), 3793–3813. https://doi.org/10.3390/ijerph120403793.

Hardell, L., Carlberg, M., 2015b. Mobile phone 1and cordless phone use and the risk for glioma - Analysis of pooled case-control studies in Sweden, 1997–2003 and 2007–2009. Pathophysiology 22 (1), 1–13. https://doi.org/10.1016/j.pathophys.2014.10.001.

Hill, A.B., 1965. The environment and disease: association or causation? J. R. Soc. Med. 108 (1), 32–37. https://doi.org/10.1177/0141076814562718.

Huser, V., Shmueli-Blumberg, D., 2018. Data sharing platforms for de-identified data from human clinical trials. Clin. Trials 15 (4), 413–423. https://doi.org/10.1177/1740774518769655.

Huss, A., Egger, M., Hug, K., Huwiler-Müntener, K., Röösli, M., 2007. Source of funding and results of studies of health effects of mobile phone use: systematic review of experimental studies. Environ. Health Perspect. 115 (1), 1–4. https://doi.org/10.1289/ehp.9149.

Institute of Medicine. Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk. Washington (DC): National Academies Press (US); April 20, 2015. 10.17226/18998.

Moskowitz, J.M., 2022. RE: Cellular Telephone Use and the Risk of Brain Tumors: Update of the UK Million Women Study. J. Natl Cancer Inst. https://doi.org/10.1093/jnci/djac109.

Moskowitz JM, Myung SK, Choi YJ, Hong YC. Reply to Brzozek et al. Comment on "Choi et al. Cellular Phone Use and Risk of Tumors: Systematic Review and Meta-Analysis. Int. J. Environ. Res. Public Health 2020, 17, 8079". Int. J. Environ. Res. Public Health. 2021 May 24;18(11):5581. 10.3390/ijerph18115581.

Nadler DL, Zurbenko IG. Estimating cancer latency times using a Weibull model. Advances in Epidemiology. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015-2019. Neuro Oncol. 2022 Oct 5;24(Suppl 5):v1-v95. 10.1093/neuonc/noac202.

Philips, A., Henshaw, D.L., Lamburn, G., O'Carroll, M.J., 2018. Brain Tumours: Rise in Glioblastoma Multiforme Incidence in England 1995–2015 Suggests an Adverse Environmental or Lifestyle Factor. J. Environ. Public Health 24 (2018), 7910754. https://doi.org/10.1155/2018/7910754.

Röösli, M., Lagorio, S., Schoemaker, M.J., Schüz, J., Feychting, M., 2019. Brain and Salivary Gland Tumors and Mobile Phone Use: Evaluating the Evidence from Various Epidemiological Study Designs. Annu. Rev. Public Health 1 (40), 221–238. https://doi.org/10.1146/annurev-publhealth-040218-044037.

Schüz, J., Elliott, P., Auvinen, A., Kromhout, H., Poulsen, A.H., Johansen, C., Olsen, J.H., Hillert, L., Feychting, M., Fremling, K., Toledano, M., Heinävaara, S., Slottje, P., Vermeulen, R., Ahlbom, A., 2011. An international prospective cohort study of mobile phone users and health (Cosmos): design considerations and enrolment. Cancer Epidemiol. 35 (1), 37–43. https://doi.org/10.1016/j.canep.2010.08.001.

Schüz J, Jacobsen R, Olsen JH, Boice JD Jr, McLaughlin JK, Johansen C. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. J Natl Cancer Inst. 2006 Dec 6;98(23):1707-13. 10.1093/jnci/djj464.

Schüz J, Pirie K, Reeves GK, Floud S, Beral V; Million Women Study Collaborators. Cellular Telephone Use and the Risk of Brain Tumors: Update of the UK Million Women Study. J. Natl. Cancer Inst. 2022 May 9;114(5):704-711. 10.1093/jnci/djac042.

Setia, M.S., 2016. Methodology Series Module 1: Cohort Studies. Indian J. Dermatol. https://doi.org/10.4103/0019-5154.174011.

Söderqvist, F., Carlberg, M., Hardell, L., 2012. Review of four publications on the Danish cohort study on mobile phone subscribers and risk of brain tumors. Rev. Environ. Health 27 (1), 51–58. https://doi.org/10.1515/reveh-2012-0004.

van Nierop, L.E., Röösli, M., Egger, M., Huss, A., 2010. Source of funding in experimental studies of mobile phone use is health: Update systematic review of funding sources and experimental studies on health effects of mobile phone: Update of a systematic review. Phys. Rep. 11 (9–10), 622–627. https://doi.org/10.1016/j.crhy.2010.10.002.

Wall, S., Wang, Z.M., Kendig, T., Dobraca, D., Lipsett, M., 2019. Real-world cell phone radiofrequency electromagnetic field exposures. Environ. Res. 171, 581–592. https://doi.org/10.1016/j.envres.2018.09.015.

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