Environment International 189 (2024) 108808

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

# Response to the letter to the editor regarding "Mobile phone use and brain tumour risk — COSMOS, a prospective cohort study"

ARTICLE INFO

*Keywords*
Cell phones
Radiofrequency Fields
Electromagnetic Fields
Non-Ionizing Radiation
Brain Neoplasms
Cohort study

Moskowitz and colleagues discuss various aspects of our study on mobile phone use and brain tumour risk (Feychting et al., 2024a). While their comments are numerous, they appear sometimes inconsistent and contradictory, and do not effectively challenge our methods or findings.

## 1. Improved exposure assessment compared to previous studies

The authors criticise the use of self-reported information to assess frequency and duration of mobile phone calls, although they do not suggest an alternative way to collect such data. For studies on solid cancer outcomes, which may take many years to develop, self-report remains the only available source of historical mobile phone exposure information. Given the well documented difficulties in assessing this information accurately (Bouaoun et al., 2024; van Wel et al., 2024; Vrijheid et al., 2006; Vrijheid et al., 2009), as its recall is challenging, COSMOS developed an assessment of self-reported mobile phone use that combines the advantages and minimizes the disadvantages of past cohort and case-control studies, as evidenced by our exposure assessment validation study (Reedijk et al., 2024; Toledano et al., 2018). The only exceptions to using self-reported mobile phone use are the Danish cohort study (Frei et al., 2011; Johansen et al., 2001; Schuz et al., 2006) and a Finnish nested case-control study (Auvinen et al., 2002), both of which relied on mobile phone subscriptions for exposure assessment and had no information about the amount of phone use and how the phone is used. Exposure assessment was considerably improved in COSMOS compared to previous studies, because in COSMOS, participants reported their historical mobile phone use habits prospectively, i.e. before tumour diagnosis, preventing differential recall bias which is a severe limitation in case-control studies of mobile phone use (Vrijheid et al., 2009). Differential recall bias is evident in several reports making interpretation of case-control studies challenging. For example, the (Interphone Study Group, 2010) reported more implausible number of hours of mobile phone use among brain tumour cases than controls. Hardell and colleagues observed the highest risk estimates for start years that were earlier than the introduction of hand-held mobile phones (Hardell et al., 2013), i.e. a time period when radiofrequency electromagnetic field (RF-EMF) exposure to the head would have been very low. Also the raised risk estimates for ipsilateral mobile phone use after very short periods since first starting mobile phone use combined with reduced risk estimates for contralateral mobile phone use are evidence of differential recall bias (Schuz, 2009). That cases had a larger variance in the reporting error of past mobile phone use was recently shown as the most likely bias introducing a spurious association in heavy mobile phone users (Bouaoun et al., 2024). See our paper for further discussions about limitations of retrospective self-reported exposure assessment in the case-control studies (Feychting et al., 2024a). Thus, the prospective collection of exposure information in COSMOS is a key strength, together with the use of objective operator data from a subsample of participants to improve the exposure estimation based on recall alone. These data were used to calibrate the self-reported mobile phone use, leading to more accurate estimation of the relation between mobile phone use and health outcomes (Reedijk et al., 2024).

Moskowitz and colleagues criticise the exposure categorisation used in our analyses but failed to mention that to pro-actively address such concerns we demonstrated that the results were independent of the choice of cut-points, as we presented analyses with cut-points based on different distributions (tertiles, quartiles, the 90th percentile), in addition to analyses where the exposure was treated as a continuous variable, with consistent null findings in all these analyses.

Moskowitz and colleagues criticise the lack of updated exposure information during the follow-up time (median 7.12 years), and the lack of information about specific wireless technologies and exposure from other RF-EMF sources. As we discuss in our paper (Feychting et al., 2024a), the RF-EMF exposure levels emitted during mobile phone calls have decreased with each new generation of mobile phone technology. Exposure levels to the head from the 1st and 2nd generations of wireless technologies are orders of magnitude higher than those of later generations and DECT phones, Wi-Fi, and base stations (van Wel et al., 2021). From numerous incidence time trend studies, e.g. (Deltour et al., 2009; Deltour et al., 2022; Little et al., 2012; Villeneuve et al., 2021) and the early prospective cohort studies of mobile phone subscribers (Johansen et al., 2001; Schuz et al., 2006), it is well established that recent mobile

https://doi.org/10.1016/j.envint.2024.108808
Received 31 May 2024; Accepted 7 June 2024
Available online 8 June 2024

phone use is not associated with an increased glioma incidence, and the remaining uncertainty is whether long-term use may affect glioma risk. For solid tumours like brain tumours, it is not exposure during the most recent years prior to diagnosis that is etiologically relevant, so the use of historical data on mobile phone use combined with baseline information is extremely important.

Moskowitz and colleagues also criticise the lack of a completely unexposed group. Today, close to 100 % of the populations in the included countries are mobile phone users. The tiny proportion of non-users is likely to differ from the mobile phone users in many other aspects, and confounding and random variation would be major problems in analyses with non-users as reference group. Comparing low vs. high or long-term vs. short-term exposures is common in epidemiological studies when exposures are prevalent, and internal comparisons within the cohort ensures comparability in the quality of outcome, exposure and confounding information. In future updates of the follow-up of health outcomes in COSMOS, information about specific wireless technologies will be more relevant. The availability of operator data will allow us to estimate the proportion of call time with, e.g., 2G or 3G technologies, which are used in parallel. As the phone switches automatically between these, it is impossible for study participants to know which technology their mobile phone uses. Any attempt to ask participants to estimate the time they have used, for example, a 3G phone is flawed (Hardell et al., 2013).

## 2. Complete outcome ascertainment

The critique by Moskowitz and colleagues regarding outcome ascertainment in the COSMOS study appears contradictory. They suggest that the incidence is likely underreported, yet also state that glioma incidence was rather high in the COSMOS study. To support their claim of underreported incidence, they cite a commentary by Hardell and Carlberg (Hardell and Carlberg, 2015), which has been refuted (Ahlbom et al., 2015). Hardell and Carlberg argued that the incidence of brain tumours is underreported in the Swedish Cancer Register due to an increase in mortality from 'tumours of uncertain or unknown behaviour of the brain' in the Swedish Cause of Death Register and hospitalizations reported in the National Patient Register. However, this claim overlooked an administrative change in the Cause of Death Register routines that entirely explained the increase in unspecified tumour mortality. It also disregarded that yearly reports in the Patient Register include prevalent cases and cannot distinguish metastases from primary tumours. The underreporting of malignant brain tumours in the Swedish Cancer Register is very low in the age groups included in COSMOS and has decreased among the elderly in recent decades (Tettamanti et al., 2019).

While it is known that meningioma – a mostly benign tumour – is under-reported in the national cancer registries, we would not expect differential under-reporting based on historical mobile phone use which would not be known to treating physicians or the registries (Larjavaara et al., 2008; Tettamanti et al., 2019).

Moskowitz and colleagues calculate the crude glioma incidence rate in COSMOS (149 observed glioma cases divided by 1,836,479 person-years; 8.11/100,000), and compare this to the overall global estimate for developed countries that includes all ages, reported by (Bondy et al., 2008). This is not a valid comparison. A more recent publication from the Central Brain Tumor Registry of the United States (CBTRUS) (Ostrom et al., 2023), covering approximately the same time period as the case recruitment in COSMOS, shows an age adjusted incidence rate of 8.5/100,000 for malignant brain tumours among persons $\geq$ 20 years. To obtain a more precise estimate of the expected number of glioma cases in the COSMOS study, we would need national population estimates of age- and sex-specific incidence rates for glioma, as defined by ICD-O-3, from the cancer registers in all included countries. However, these estimates would still refer to the same cancer registries that the COSMOS cohort used to identify incident brain tumour cases during follow-up. Furthermore, as is common in cohort studies, we reported all effect estimates from internal comparisons within the COSMOS cohort rather than comparing to external rates.

## 3. Other considerations

Moskowitz and colleagues criticise the limited statistical power of our analyses and claim that we have observed fewer cases than expected from our earlier power calculations. However, these were made for all brain tumours combined (Schuz et al., 2011), while Moskowitz and colleagues compare them to the observed number of glioma cases. A more accurate calculation should include all brain tumour cases and shows that the observed number of cases is very close to that expected from the power calculations, bearing in mind that only crude incidence estimates can be calculated. As we discuss in our article and in response to a previous letter to the editor (Feychting et al., 2024a; Feychting et al., 2024b), statistical power is the main current limitation of our study, especially for acoustic neuroma and meningioma. Therefore, additional follow-up of the COSMOS cohort by linkage to cancer registers is warranted in the future. In the meantime, the pooled analysis of glioma risk estimates from all prospective cohort studies for mobile phone use $\geq$ 10 years shows an effect estimate with the upper confidence boundary at 1.04 (see Supplementary Table S9 in our paper) (Feychting et al., 2024a).

Moskowitz and colleagues raise questions about access to our data. According to national laws and regulations in participating countries, individual-level sensitive data can be made available only where legal requirements for access to personal sensitive data can be met. Please contact the corresponding authors for further questions about data access.

COSMOS was funded through grant applications to publicly funded research councils or organisations, undergoing the same rigorous and competitive evaluation process as other research grant applications. In some countries, industry complemented the funding either through national research programs led by public authorities without any influence from industry, or by using trusted public authorities as a firewall, with agreements that guaranteed the independence of the researchers. It is reasonable that industry contribute to the costs of research into potential health effects of their products, as long as it can be guaranteed that they have no influence on the conduct of the research, and this independence was fully the case in COSMOS.

In conclusion, while Moskowitz and colleagues raise several points regarding our study on mobile phone use and brain tumour risk, their criticisms do not undermine the robustness of our methodology or the validity of our findings. Our use of prospective data collection, rigorous exposure assessment, and independent funding ensures that the COSMOS study provides reliable and objective insights into the potential health effects of mobile phone use.

## Funding

The Swedish part of COSMOS was supported by the Swedish Research Council (50096102); AFA Insurance (T-26:04); the Swedish Research Council for Health, Working Life and Welfare (2010-0082, 2014-0889); the Swedish Radiation Safety Authority (SSM2015-2408); and VINNOVA (P31735-1). VINNOVA received funds for this purpose from TeliaSonera AB, Ericsson AB and Telenor Sverige AB, to cover part of the data collection (funding ended 2012). The provision of funds to the COSMOS study investigators via VINNOVA was governed by agreements that guarantees COSMOS' complete scientific independence.

The Danish part of COSMOS was funded by the Danish Strategic Research Council [grants 2103–05-0006/2064–04-0010].

The Finnish cohort has previously been supported by funding from the National Technology Agency (TEKES), with contributions to the research program but no control of the use of funding from Nokia,

mobile network providers TeliaSonera and Elisa; Pirkanmaa Hospital District competitive research funding (grant no. VTR 9 T003); Yrjö Jahnsson Foundation (grant no. 5692); Kone Foundation, and an unrestricted grant from Mobile Manufacturers' Forum (with Pirkanmaa Hospital District as a firewall) with a contract guaranteeing the complete scientific independence of the researchers to analyse, interpret and report the results with no influence for the funding sources.

The UK part of COSMOS was supported for an initial 5-year period by the Mobile Telecommunications and Health Research (MTHR), an independent programme of research into mobile phones and health jointly supported by the UK Department of Health and the mobile telecommunications industry (project reference number 091/0006) and, subsequently, funded by the UK Department of Health & Social Care via its Policy Research Programme (project reference number PR-ST-0713–00003); as well as by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Health Impact of Environmental Hazards at King's College London in partnership with Public Health England (now UK Health Security Agency, UKHSA) and Imperial College London (HPRU-2012–10141) and subsequently the NIHR HPRU in Chemical and Radiation Threats and Hazards at Imperial College London and UK HSA (grant award reference NIHR-200922). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health & Social Care or the UK HSA. PE is Director of the MRC Centre for Environment and Health supported by the Medical Research Council and Public Health England (MR/L01341X/1, 2009–2019 and solely by the Medical Research Council MR/S019669/1, 2019-; and Director of the NIHR HPRU in Chemical and Radiation Threats and Hazards at Imperial College London. PE acknowledges support from the NIHR Imperial Biomedical Research Centre. PE is a UK Dementia Research Institute (DRI) group leader, UK DRI at Imperial College London (DRI is funded by the Medical Research Council, Alzheimer's Society and Alzheimer's Research UK) and also acknowledges funding from Health Data Research UK (HDR UK). MBT's Chair and RBS's fellowship are supported by a donation from Marit Mohn to Imperial College London to support Population Child Health through the Mohn Centre for Children's Health and Wellbeing.

The Dutch part of the COSMOS study was supported by The Netherlands Organization for Health Research (ZonMW) within the programme Electromagnetic Fields and Health Research, under grant numbers 85200001, 85500003, 85,200,002 and 85800001.

The French part of COSMOS is funded by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), project reference number 2013-CRD-17, 2015-CRD-30, 2018-CRD-03, 2020-CRD-RF20-01 and the International Agency for Research on Cancer.

All financial support for the submitted work is described above; there are no financial relationships with any organizations that might have a commercial interest in the submitted work, nor any other relationships or activities that could appear to have influenced the submitted work.

**Note:** Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

## CRediT authorship contribution statement

**Maria Feychting:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Joachim Schüz:** Conceptualization, Writing – review & editing. **Mireille B. Toledano:** Writing – review & editing. **Roel Vermeulen:** Writing – review & editing. **Anssi Auvinen:** Writing – review & editing. **Aslak Harbo Poulsen:** Writing – review & editing. **Isabelle Deltour:** Writing – review & editing. **Rachel B. Smith:** Writing – review & editing. **Joel Heller:** Writing – review & editing. **Hans Kromhout:** Writing – review & editing. **Anke Huss:** Writing – review & editing. **Christoffer Johansen:** Writing – review & editing. **Giorgio Tettamanti:** Writing – review & editing. **Paul Elliott:** Conceptualization, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

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

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