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Response to the letter from members of the ICBE-EMF

1. To the Editors

Re: Frank et al. The Systematic Review on RF-EMF Exposure and Cancer by Karipidis et al. (2024) has Serious Flaws that Undermine the Validity of the Study's Conclusions

We strongly disagree with the assertions and conclusions made by Frank et al. as we were comprehensive and transparent with our systematic review and *meta*-analytic approach, which has been peer-reviewed by multiple experts in the area. We can only review and analyse the available evidence and we have highlighted that there are limitations to the included studies and data which has some impact on the ability to draw definitive conclusions; hence, our rating of "moderate certainty evidence" that near field RF-EMF exposure to the head from mobile phone use likely does not increase the risk of glioma, meningioma, acoustic neuroma, pituitary tumours, and salivary gland tumours in adults, or of paediatric brain tumours.

Frank et al. wrongly mention that we did not declare any competing interests, as these are listed at the end of the paper. Frank et al. further attempt to discredit ICNIRP. ICNIRP is recognised by the World Health Organization and other international and national authorities as the peak international body for providing advice on the effects of non-ionizing radiation. ICNIRP is a non-profit scientific body and does not receive any funds from industry (ICNIRP, 2022). In that context the authors of the letter have not made any declaration of interest although several of the letter's co-authors have undeclared conflicts of interest (COI) (de Vocht and Albers 2022; de Vocht and Albers 2024), according to the definition of COI developed by the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors (ICMJE) 2024), in line with COPE recommendations (https://publicationethics.org/competinginterests), adhered to by Environment International and any other Elsevier journals (https://service.elsevier.com/app/answers/detail/a_id/286/supporthub/publishing/).

Frank et al. also state false accusations that some co-authors of our systematic review had links to the telecommunications industry. To be clear, there are no links between any of the authors in our systematic review and the telecommunications industry.

We have addressed the five specific points raised by Frank et al. below to hopefully obviate potential misunderstandings that their letter may generate:

2. Studies included in the systematic review

Given the observational nature of epidemiological studies there is always inherent limitations in this line of evidence and we included a detailed sub-section in the Discussion of our paper on limitations in the available evidence. This is reflected in the initial rating of "moderate" confidence to all the included studies in our systematic review as per the OHAT GRADE-based guidelines (NTP-OHAT 2019).

Specifically on the Interphone case-control studies, the criticisms raised in the review by (Choi et al. 2020) have been rebutted in multiple publications (Brzozek et al. 2020; de Vocht and Roosli 2020). De Vocht and Roosli (2020) pointing out that the INTERPHONE team spent considerable effort trying to evaluate whether observed increased and decreased risks could be the result of recall and selection biases (Vrijheid et al. 2009a; Vrijheid et al. 2009b), and a recent study found some indication for reverse causality as an explanation for seemingly protective effects from mobile phone use (Olsson et al., 2019).

Studies with prospective exposure assessment (preceding and independent of outcome ascertainment) – typically of cohort design such as the Danish study (Frei et al. 2011; Schüz et al. 2011) or the UK Million Women study (Schuz et al. 2022) – are immune from recall bias. Moreover, the authors of the Danish cohort study have validated the subscriber status of 1355 cohort members against the mobile phone use reported by as many participants in the Danish Interphone study (Schuz and Johansen 2007); 61 % of subscribers were indeed mobile phone users, and 16 % of the nonsubscribers were actually regular mobile phone users before 1996. In the paper reporting on the second follow-up of the cohort (Schüz et al. 2006), the authors estimated that the exposure misclassification (random by default in a cohort study) would have slightly diluted a possible true association (an attenuated estimate of 1.2 when the actual relative risk is 1.5, and an attenuated relative risk of 1.09 when the actual relative risk is 1.2); however, under the null (no true association), such exposure misclassification would have only reduced the statistical power without distorting the risk estimates.

Frank et al further falsely claim that the Million Women Study (Schuz et al. 2022) suffered from high participant attrition. The Million Women Study had an attrition rate of 8.9 % out of 852,173 who completed the first survey including questions on mobile phone use, due to exclusions of subjects with cancer before survey completion, aged $\geq$ 70 years, or missing data about mobile phone use. Based on the OHAT risk of bias tool (NTP-OHAT 2015) this is acceptable handling of subject attrition including very little ($\leq$20 %) missing outcome data and the reasons for missing subjects are unlikely to be related to both outcome and exposure.

3. Dose response analysis

In addition to looking at simple exposure proxies such as "ever" versus "never," and "time since start of use", our systematic review looked at various dose-related exposure metrics for mobile phone use, including the number of years of use, and the lifetime intensity of use including cumulative call time and the cumulative number of calls. As reported in our systematic review the dose–response *meta*-analyses did not show a statistically significant increase in risk with either

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cumulative call time or cumulative number of calls. Our dose–response *meta*-analyses is scientifically state of the art and the methodology of this type of analysis is well reported (Crippa et al. 2019; Orsini and Spiegelman 2020; Orsini 2021). A dose–response *meta*-analysis takes into account the distribution of the dose and how it is varying across studies.

Frank et al falsely claim that critical information such as the goodness-of-fit is missing from our dose–response analysis. Statistical models used for dose–response *meta*-analysis are not linear regression models commonly used with individual data points, so goodness of fit is not an appropriate measure here (Orsini and Spiegelman 2020).

Frank et al. mention a newly published *meta*-analysis (Moon et al. 2024), which they consider is based on "better epidemiological methodology", and "finds (in Figure 2) that higher levels of CCT (greater than 896 h) are associated with a statistically significantly higher relative risk of 89 brain tumours (OR 90 1.59, 95 % CI 1.25–2.02)". We strongly disagree with this opinion; a few of the numerous criticalities of this quantitative synthesis are underlined below, focussing on the *meta*-analyses by cumulative call time. First of all, the decision to focus on the highest exposure contrast contradicts the general aim of any categorical dose–response analysis, which is to look at possible trends in risk with increasing exposure. Several in-depth analyses have indicated that the highest exposure group in case-control studies is particularly sensitive to recall bias and thus overestimation of the risk (Röösli et al. 2019). Furthermore, the choice of the cutoff (>896 h) is arbitrary, and the study-specific exposure categories vary widely across studies. Most important, the included measures of effect in the cited paper (Moon et al. 2024) seem to be data driven based on the findings rather than on uniform criteria.

As clearly mentioned in our systematic review, we repeat again here that the preferred side of the head for mobile phone use is an important exposure determinant but, when assessed retrospectively through self-report, is affected by substantial misclassification and recall bias (Goedhart et al. 2015a; Goedhart et al. 2015b; Goedhart et al. 2018; Inyang et al. 2010; Kiyohara et al. 2016; Kiyohara et al. 2018), as also indicated by concurrent observations of increased risk for ipsilateral mobile phone use and protective effect for contralateral use; i.e. in certain studies with no overall association, there was an increased risk with ipsilateral use which was compensated by a decreased risk with contralateral use, indicating a bias (Schüz 2009). Due to such a poor validity, self-reported laterality of mobile phone use was not included among the exposure metrics and contrasts examined in our systematic review.

4. Reference to time-trend simulation studies

We understand the limitations of time-trend simulation studies, including the inability to account for patterns in mobile phone use on the individual level. As such, we agree that these studies, on their own, cannot be used to make causal inferences, but can be used as complementary evidence to check the consistency of the results from aetiological study designs; i.e. showing that the increased risks observed in some case-control studies were incompatible with the actual incidence rates of glioma/brain cancer observed in several countries and over long periods. This is in line with the recommendations for the conduct of systematic reviews in toxicology and environmental health research – COSTER (Whaley et al. 2020), and clearly explained in section 3.1.5.3 of our paper.

For this complementary evidence we only used time-trend studies that also conducted a simulation analysis, i.e., assessed the external plausibility of findings from analytical studies of specific CNS tumour risks in relation to mobile phone use, by comparing predicted and observed time-trends of incidence rates. None of the time-trend studies mentioned by Frank et al. included a simulation analysis [i.e., (Davis et al. 2020; Hardell and Carlberg, 2017; Philips et al. 2018; Zada et al. 2012). In some of these studies, increases in the rates of morphological or site-specific brain cancer sub-types are highlighted (such as shown for glioblastoma multiforme by Phillips et al. 2018 for example) but are actually accompanied by decreases in brain cancers of unspecified site and/or morphology, while overall brain cancer incidence has remained largely unchanged. This suggests improvements in diagnostic techniques as the reason for increasing trends in certain brain cancer subtypes. There have also been shifts in classifying sub-types in updated editions of the WHO classification of tumours of the central nervous system; for example, the WHO 2000 classification induced a shift from anaplastic astrocytoma to glioblastoma. This is addressed in many of the included time-trend simulation studies, e.g. in (Choi et al. 2021; Karipidis et al. 2018) where reclassification of unclassified or overlapping brain cancers was shown to reduce increased trends in morphological or topological sub-types (such as in glioblastoma multiforme).

5. Cancer risk after longer latent periods following exposure

The exact causes of brain cancer are unknown and so is the latency period for the disease. Ionising radiation has been shown to induce brain cancer by causing DNA damage with a latency period of about 5 or more years (UNSCEAR 2009) and it is standard in epidemiological studies on ionizing radiation and solid tumours to use a latency period for ten years [e.g., (Richardson et al. 2023)]. RF-EMF exposure is non-ionising radiation which does not cause direct DNA damage, and it has been argued that a possible effect would have a latency shorter than 5 years (Little et al. 2012). However, it has also been argued that the latency for an increased risk of brain cancer could be both short and long, indicating tumour initiation and promotion, respectively (Morgan et al. 2015).

Our systematic review defines long latency as 10 years or more, which captures all the available evidence. There is inadequate evidence available to pool results and analyse latency of 15 years or more. Published time trends analyses do not indicate any noticeable increase in brain tumour incidence since the introduction of mobile phone use as mentioned earlier. Current time trend analyses would not yet pick up a risk increase occurring at latency periods of more than 15–20 years (Röösli et al. 2019). However, assuming a similar latency for non-ionizing radiation as observed for ionizing radiation, one would expect that any relevant risk should already have started to emerge by now (Röösli et al. 2019).

6. Methodology for pooling results in a *meta*-analysis

Our systematic review included a number of different analyses in assessing the certainty in the evidence. For example, when looking at ever or regular mobile phone use and glioma, pooling the results from all the included studies did indeed show substantial heterogeneity across studies ($I^2 = 62$ %). Strikingly, a subgroup analysis of studies with low risk of bias showed no heterogeneity ($I^2 = 5.47$ %) with similar results when looking at the contrast of time since first mobile phone use.

According to the Cochrane handbook for systematic reviews (Higgins et al. 2021) two studies is a sufficient number to perform a *meta*-analysis, provided that those two studies can be meaningfully pooled and provided their results are sufficiently similar. However, a *meta*-analysis with only two studies may not have a large enough sample size to draw conclusions or provide new knowledge. Therefore, in our systematic review we set a minimum of three studies for amenability to a *meta*-analysis. It is important to note that the majority of main analyses in our systematic review included more than five studies anyway.

7. Conclusion

Our systematic review provided a comprehensive, evidence-based analysis of the potential link between RF-EMF exposure and cancer, addressing a highly debated issue with scientific rigor and transparency. The review was marked by a clear focus on methodological robustness following established guidelines and best practices in systematic review methodology. The findings of our systematic review are therefore

appropriate recognizing also the limitations in the current evidence.

Support

This project was commissioned and partially funded by the World Health Organization (WHO), and this review was partially funded by the WHO radioprotection programme. Co-financing was provided by the New Zealand Ministry of Health; the Istituto Superiore di Sanità in its capacity as a WHO Collaborating Centre for Radiation and Health; and ARPANSA as a WHO Collaborating Centre for Radiation Protection.

CRediT authorship contribution statement

Ken Karipidis: Conceptualization, Writing – original draft. **Dan Baaken:** Writing – review & editing. **Tom Loney:** Writing – review & editing. **Maria Blettner:** Writing – review & editing. **Rohan Mate:** Writing – review & editing. **Chris Brzozek:** Writing – review & editing. **Mark Elwood:** Writing – review & editing. **Clement Narh:** Writing – review & editing. **Nicola Orsini:** Writing – review & editing. **Martin Röösli:** Writing – review & editing. **Marilia Silva Paulo:** Writing – review & editing. **Susanna Lagorio:** Writing – original draft.

Declaration of competing interest

Ken Karipidis as part of his employment is involved in the provision of advice to the Australian Commonwealth Government, Australian States and Territories and the general public on the risks and health effects of exposure to ionising and non-ionising radiation. He is also a member of the International Commission on Non-Ionizing Radiation Protection where he contributes in the development and dissemination of science-based advice on limiting exposure to non-ionizing radiation.

Mark Elwood has given expert advice on topics in electromagnetic fields and health, and on the objective interpretation of epidemiological and other scientific information, over many years to individuals and groups, including government ministries, environmental regulators, community groups, commercial organisations, and formal inquiries by government and professional groups including parliamentary and legal proceedings. Some of this work has been financially supported, by universities, health care organisations, research bodies, or by government, professional or commercial groups. Some work has been reported 'blind', with the client being unidentified.

Susanna Lagorio was principal investigator (April 2019 – March 2020) of the research project "BRiC 2018/06 – Systematic reviews of exposure to radiofrequency fields and cancer", supported by the Italian Workers' Compensation Authority, a public no-profit entity (grant code I85B19000120005). Her employment duties involved provision of advice on health hazards from exposure to RF-EMF to the Italian Ministry of Health and Higher Health Council (she retired on August 1st, 2023).

Martin Röösli's research is entirely funded by public entities or not for profit foundations. He has served as advisor on potential health effects of exposure to non-ionizing radiation to several national and international public advisory and research steering groups, including the World Health Organization, the International Agency for Research on Cancer, the International Commission on Non-Ionizing Radiation Protection, the Swiss Government (member of the working group "Mobile phone and radiation" and chair of the expert group BERENIS), the German Radiation Protection Commission (member of the committee Non-ionizing Radiation (A6) and member of the working group 5G (A630)) and the Independent Expert Group of the Swedish Radiation Safety Authority. From 2011 to 2018, M.R. was an unpaid member of the foundation board of the Swiss Research Foundation for Electricity and Mobile Communication, a non-profit research foundation at ETH Zurich. Neither industry nor nongovernmental organizations are represented on the scientific board of the foundation.

Chris Brzozek and Rohan Mate as part of their employment are involved in the provision of advice to the Australian Commonwealth Government, Australian States and Territories and the general public on the risks and health effects of exposure to ionising and non-ionising radiation.

The other authors declare that they have no known conflicts of interest.

Data availability

Data will be made available on request.

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