Appendix 2

We observed an overall decrease in risk of glioma and of meningioma with any regular use of a mobile phone (main text Table 2). One means of correcting, at least crudely, for downward bias in the risk estimates for mobile phone use might be to undertake analyses using the lowest category of users as the reference category for risk estimates in higher categories. We present here INTERPHONE results obtained using this approach and discuss their justification and issues in their interpretation.

Material and Methods

These analyses were confined to INTERPHONE participants who were ever regular users of a mobile phone and were done using as reference categories the lowest categories of time (years) since first regular use, cumulative number of calls and cumulative duration of calls (see main text Table 2). They included only matched sets where both the case and the control(s) were regular users. As in the main analyses, we estimated odds ratios (OR) and their respective 95% confidence intervals (CI) using conditional logistic regression for matched sets.

Results

The total study base for these analyses was 1211 glioma cases (44.7% of subjects used in the main analysis), 1251 glioma controls (42.1%), 842 meningioma cases (35.0%) and 854 meningioma controls (32.1%). For meningioma, the ORs for each category of each variable remained below 1.0 except in the highest category of cumulative call time (see Table). In contrast, the ORs for glioma were, with few exceptions, all above 1.0 and the highest odds ratios were found in one of the two highest exposure categories for each variable. The greatest increase was with increasing time since start of use of a mobile phone.

Discussion

In assessing the effects of environmental exposures in epidemiological studies, the estimated risk in a given exposure category is generally evaluated relative to the risk in unexposed people. This approach is clearly appropriate when exposed and unexposed subjects are similar in all respects except the exposure of interest; bias can occur, however, when this is not the case (1). Dissimilarity between exposed and unexposed subjects can result from differences in selection factors, such as a higher refusal rate among unexposed than exposed subjects, or from the presence of an important confounder distinguishing exposed from unexposed subjects that has not been measured or not controlled. In such situations, analyses excluding unexposed subjects have been recommended (1;2).

Analyses of the INTERPHONE non-response questionnaire suggest the presence of participation bias: less participation of non-users of mobile phones than users (3). In addition, controls were less likely to participate than cases. A simulation study taking these biases into account has shown that they could lead to a J-shaped exposure-response relationship (4). Given the penetration of mobile phone technology at the time of the INTERPHONE study it is also reasonable to speculate that non-regular mobile phone users differed from regular users with respect to a number of unmeasured factors, some of which might have been confounding. If the most appropriate reference group is unclear a priori, as these considerations suggest it might reasonably have been, it has been recommended that analyses are done using both reference groups (unexposed and lowest exposed) to see if the results depend on inclusion of the

unexposed group and, if so, this fact should be reported (2). The use of the lowest exposed as a reference group was not an a priori decision in this case, however.

Restricting analyses to regular users to correct for apparent downward bias in risk estimates caused by participation bias assumes that this bias (less frequent participation by non-users) is the main reason for the bias in risk estimates. It assumes also that participation bias affects comparisons of non-users with users but not comparisons of different times since start of use or levels of cumulative use *in users*. Neither of these assumptions is necessarily correct.

If participation bias were the main reason for reduced odds ratios in recent or light users relative to non-users, the reduction would be expected to be less in study centres with higher participation rates. There is, however, no clear trend in this direction. ORs well below unity were observed in the lowest regular use category as much in centres with the highest participation rates as in centres with the lowest (Appendix Table 6); and there are centres with high and with low participation rates among the few in which ORs in this exposure category were close to or above unity.

There is also evidence in our data that participation bias may affect the distributions of time since start of use of a mobile phone. In analyses of the INTERPHONE non-responder questionnaire, not only did we observe a higher proportion of regular mobile phone users among participants but we also observed, in regular users, that participants tended to be earlier regular users than non-participants (Table 4 in (3)). If this observation reflects a general pattern, it provides evidence for greater participation bias in recent regular users than in longer-term regular users. Failure to take account of this pattern when correcting for bias could lead to overestimation of ORs in longer-term users, because their OR which is less affected by bias would be "corrected" with the same factor as the OR for the recent regular users, which was more affected by bias.

There is another observation that suggests that participation bias may not be the main reason for the observed low odds ratios. In Table 2 of the main text, the reductions in the ORs for glioma in the lowest exposure categories are much greater than those for meningioma. For example, the OR for glioma at 1-1.9 years since first use is 0.62 (95% CI 0.46-0.81) while that for meningioma is 0.90 (95% CI 0.68-1.18); each point estimate is not within the 95% confidence interval of the other. The contrast is similar but not as great for the lowest categories of cumulative call-time and number of calls.

Prodromal symptoms could, perhaps, explain this greater risk reduction in the lowest exposure categories for glioma than for meningioma by making cases less likely to take up regular mobile phone use close to the time of diagnosis of the glioma (reverse causation). While little has been published on the duration and effects of prodromal symptoms of brain tumours, there is evidence that epilepsy is strongly associated with and can precede subsequent glioma by up to 10 years (5). There is a similar but much weaker association of epilepsy with subsequent meningioma. Thus an impact of prodromal symptoms on uptake of mobile phones that is greater for glioma than for meningioma is plausible. If prodromal symptoms rather than participation bias explained the low relative risks in short-term users, then restricting analyses to regular users would introduce upward bias in odds ratios for the higher exposure categories.

Disregarding the issues raised above, the Table could be taken to suggest that mobile phones increase risk of glioma but not of meningioma; but there are some discordant patterns in these

results. First, ORs for meningioma that are well below unity persist in lower levels of cumulative use of mobile phones. It seems implausible that mobile phone use would increase the risk of glioma but decrease the risk of meningioma, particularly at low levels of exposure. Second, the OR for glioma increases more strongly with time since start of use than with cumulative use. While it could be argued that this stronger increase is due to more accurate recall of the date of first regular use than the amount of use, an OR of 1.68 (95% CI 1.16-2.41) 2-4 years after use began seems implausible, given a very high prevalence of mobile phone use in recent years and the absence of reports of increasing incidence of malignant brain tumours (mainly gliomas) in people under 65 years of age, where use is greatest (6-8). Third, in the results using never regular users as the reference category (main text Table 2) and the results presented here, there is little or no upward trend in ORs for glioma across the first eight or nine deciles of cumulative call time and cumulative number of calls; and the only materially increased OR was in the highest exposure category (the tenth decile) for cumulative call time. This exposure category includes some highly implausible reported values of mobile phone use (e.g., 12+ reported hours of use per day), which were more common in glioma cases than in controls. This possible differential recall bias is not removed by changing the reference category.

Conclusion

Analyses excluding never regular users of mobile phones may have reduced downward bias in ORs for menigioma and glioma due to selective non-participation of people who were never regular users. There is evidence, however, of persisting bias in the results of these analyses and it is possible that the exclusion of never regular users has produced upward bias in the ORs, particularly for glioma. Thus biases and error prevent a causal interpretation of these results.

Appendix 2 Table – ORs between mobile phone use and brain tumours (meningioma and glioma separately) by time since start of regular use, cumulative call time and cumulative number of calls, excluding use with hands-free devices; analyses restricted to ever regular-users

	Meningioma					Glioma				
	Cases	Controls	OR	95 % CI		Cases	Controls	OR	95 % CI	
Time since start of regular use (years)										
1-1.9 years	116	112	1.00			93	159	1.00		
2-4	362	367	0.90	0.62	1.31	460	451	1.68	1.16	2.41
5-9	288	308	0.75	0.51	1.10	468	491	1.54	1.06	2.22
10+	76	67	0.86	0.51	1.43	190	150	2.18	1.43	3.31
Cumulative call time with no hands-free devices (hours)[1]										
<5 hours	113	88	1.00			90	114	1.00		
5.0-12.9	83	88	0.79	0.48	1.29	92	124	0.88	0.56	1.39
13-30.9	95	107	0.72	0.45	1.15	127	118	1.37	0.87	2.14
31-60.9	70	87	0.59	0.35	0.99	108	126	1.13	0.72	1.77
61-114.9	74	88	0.58	0.35	0.97	121	135	1.06	0.68	1.67
115-199.9	69	95	0.64	0.39	1.06	129	119	1.13	0.71	1.78
200-359.9	74	81	0.58	0.35	0.96	116	138	1.00	0.63	1.58
360-734.9	83	80	0.85	0.51	1.41	142	139	1.17	0.74	1.84
735-1639.9	85	69	0.81	0.49	1.36	126	125	1.09	0.69	1.72
1640+	96	71	1.10	0.65	1.85	160	113	1.82	1.15	2.89
Cumulative number of calls with no hands-free devices (in hundreds)[1]										
<1.5 x 100 calls	109	81	1.00			92	102	1.00		
1.5-3.4	86	98	0.54	0.32	0.90	91	123	0.95	0.59	1.52
3.5-7.4	92	97	0.76	0.46	1.27	108	148	0.85	0.55	1.32
7.5-13.9	88	91	0.76	0.45	1.26	121	111	1.19	0.74	1.89
14-25.4	75	107	0.56	0.34	0.92	133	134	1.10	0.70	1.73
25.5-41.4	71	72	0.60	0.35	1.02	121	124	1.19	0.75	1.88
41.5-67.9	85	94	0.63	0.38	1.05	126	122	1.02	0.64	1.62
68-127.9	102	89	0.79	0.49	1.29	136	147	1.13	0.73	1.77
128-269.9	79	63	0.76	0.44	1.32	154	120	1.49	0.94	2.36
270+	55	62	0.66	0.37	1.17	129	120	1.31	0.82	2.11

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

Reference List

(1) Greenland S, Poole C. Interpretation and analysis of differential exposure variability and zero-exposure categories for continuous exposures. Epidemiology 1995; 6(3):326-328.

(2) Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd ed. Philadelphia: Lippincott,Williams and Wilkins, 2008.

(3) Vrijheid M, Richardson L, Armstrong BK, Auvinen A, Berg G, Carroll M et al. Quantifying the impact of selection bias caused by nonparticipation in a case-control study of mobile phone use. Ann Epidemiol 2009; 19(1):33-41.

(4) Vrijheid M, Deltour I, Krewski D, Sanchez M, Cardis E. The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. Journal of Exposure Science and Environmental Epidemiology 2006; 16(4):371-384.

(5) Schwartbaum J, Johnsson F, Ahlbom A, Preston-Martin S, Malmer B, Lonn S et al. Prior hospitalization for epilepsy, diabetes, and stroke and subsequent glioma and meningioma risk. Cancer Epidemiol Biomarkers Prev 2005; 14(3):643-650.

(6) Roosli M, Michel G, Kuehni B, Spoerri A. Cellular telephone use and time trends in brain tumour mortality in Switzerland from 1969 to 2002. European Journal of Cancer Prevention 2007; 16(1):77-82.

(7) Deltour I, Johansen C, Auvinen A, Feychting M, Klaeboe L, Schuz J. Time trends in brain tumor incidence rates in Denmark, Finland, Norway and Sweden, 1974-2003. J Natl Cancer Inst 2009; e-pub ahead of print 11/24/2009.

(8) Australian cancer registry data to 2005 . 2009. http://www.aihw.gov.au/cancer/data/datacubes/index.cfm