Shanghai textile worker cohort (Astrakianakis *et al*, 2007). Although neither the modest excess relative risks observed nor the exposure–response trend for exposures >15 years since first exposure (Table 3) were statistically significant, the findings are somewhat suggestive of a possible late pro-carcinogenic effect. We do not believe that our observations on endotoxin exposure and lung cancer risk necessarily challenge a well-established association. Instead, we would argue that the exposure–response association may change over time owing to complex, yet poorly understood, underlying mechanisms. We are also not the first to report that an inverse association between endotoxin and lung cancer risk may be time varying, diminishing over time (Mastrangelo *et al*, 2005).

We have acknowledged the absence of data on risk factors other than active smoking, such as indoor air pollution from cooking fuels and diet. However, it is highly unlikely that either indoor air pollution or diet was correlated with endotoxin exposure in this cohort, and thus were probably not important confounders. Socio-economic status was relatively homogenous in the cohort, and also was unlikely to have been a confounder. Our exposure assessment for endotoxin (Astrakianakis *et al*, 2006) did take into account temporal changes in exposure levels during the cohort's relevant work experience, to the extent that available historical data permitted. Endotoxin is a highly variable exposure, and as we noted in the paper, some exposure misclassification was inevitable.

We encourage analyses that consider temporal patterns of association in other endotoxin-exposed study populations, which can provide valuable insights into disease aetiology and pathogenesis.

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Response to 'Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France'

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Sir,

The recent paper by Journy *et al* (2015) addresses an important issue regarding the interpretation of epidemiological studies of CT scans and cancer risk. It has been suggested that raised risks reported in the studies in Northern England (Pearce *et al*, 2012) and Australia (Mathews *et al*, 2013) might reflect the early symptoms of undetected cancer, or of factors that predispose to cancer and which are the indications for the CT scans, rather than an effect of the CT scans *per se* (Walsh *et al*, 2014). The study of Journy *et al*–based on a cohort of children who received CT scans at 23 radiology departments in France–benefits from the availability of information on predisposing factors for cancer. However, I have concerns that their findings could be misinterpreted.

Table 1 here combines the results from Table 5 and Supplementary Table 6 from the study by Journy *et al*. The authors have highlighted that – for each cancer type – the estimate of the excess relative risk (ERR) per 1 mGy cumulative organ dose is lower with adjustment for predisposing factors than without such an adjustment. At face value, this might suggest confounding by indication, reflecting higher cancer risk and potentially higher radiation doses from CT scanning among children with predisposing factors compared with children without such factors. However, Table 1 here also shows that – for each cancer type – the ERR among children without predisposing factors is at least as large as the unadjusted value for the cohort overall, whereas the ERR among children with predisposing factors is close to zero. This suggests that the difference between the unadjusted and adjusted values principally reflects modification of the ERR by predisposing factors, rather than confounding.

It is unclear from the study by Journy *et al* to what population the adjusted ERR estimates apply. Looking at Table 1, the adjusted estimates appear to be similar to a weighted average of the ERR estimates for those either with or without a predisposing factor, with weighting based on the numbers of cancer cases in each group. This would suggest that the adjusted estimates reflect the prevalence of predisposing factors among those children who developed cancer. However, from a public health perspective, it is more relevant to consider the prevalence of predisposing factors in the general population, rather than in the selected population

Table 1. Number of cases and associated risks of primary tumours of the CNS, leukaemia, and lymphoma

	CNS cancer				Leukaemia				Lymphoma			
	Cases	IR	ERR	95% CI[a]	Cases	IR	ERR	95% CI	Cases	IR	ERR	95% CI
All children	22	9.4			17	7.3			19	8.1		
Unadjusted for predisposing factors[b]			0.022	−0.016, 0.061			0.057	−0.079; 0.193			0.018	−0.068; 0.104
Adjusted for predisposing factors			0.012	−0.013, 0.037			0.047[c]	−0.065; 0.159			0.008	−0.057; 0.073
Children without a predisposing factor	15	6.4	0.028	n.a.	12	5.2	0.187	n.a.	12	5.2	0.025	n.a.
Children with a predisposing factor	7	565.9	−0.005	n.a.	5	128.0	−0.012	n.a.	7	160.3	−0.005	n.a.

Abbreviations: CNS = central nervous system; CI = confidence interval; ERR = excess relative risk; IR = incidence rate; n.a. = not available. The table provides the IR per 100 000 person-years, ERR related to cumulative organ dose (in mGy) from CT scans, for all children (without and with adjustment for predisposing factors), and separately for children with and without predisposing factors, with a 2-year exclusion period (based on Journy *et al*, 2015).

[a]Wald-based CI for the ERR.

[b]Factors predisposing specifically to cancer at the site specified.

[c]Listed as 0.045 in Supplementary Table 6 of Journy *et al*.

of cancer patients. Fewer than 4% of the children in the cohort of Journy *et al* had a predisposing factor and the correspondence percentage for the general population is likely to be lower still, given that children with a predisposing factor may be more likely to receive CT scans than other children. On that basis, the ERR estimates specific to children without a predisposing factor would seem to be much more relevant to the general population than the adjusted estimates of Journy *et al*.

In view of the small number of cases in this study, inferences are limited. Further follow-up of this cohort and results from other studies that collect information on predisposing factors (e.g., Meulepas *et al*, 2014) would be valuable in providing further insights. Nevertheless, the findings of Journy *et al* do not indicate that the association between cancer risk and radiation exposure from CT scans has been confounded by predisposing factors for cancer.

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Comment on 'Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France'—Evidence of confounding by predisposing factors unclear

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Sir,

The paper by Journy *et al* (2015) presents the first results of a very carefully conducted cohort study of paediatric computerised tomography (CT) patients from France, part of the European collaborative study 'EPI-CT' (Bosch de Basea *et al*, submitted). Because of criticisms raised about the results of previous studies of CT patients (Pearce *et al*, 2012; Mathews *et al*, 2013; Huang *et al*, 2014), the authors made particular efforts to collect information on potential factors which could invalidate estimates of radiation risks in these studies. The current paper emphasises, in particular, the potential impact of predisposing factors (PFs) for leukaemia, central nervous system (CNS) tumours and lymphoma, the outcomes under study in this paper. For this study, a list of PFs was developed by paediatric oncologists based on the literature, and hospitalised discharge records of cohort members were searched to identify cohort members with PFs. These included familial adenomatous polyposis, multiple endocrine neoplasia, retinocytoma, Fanconi anaemia, ataxia telangiectasia, neurofibromatosis, other phacomatoses, xeroderma pigmentosum, Down syndrome, Noonan syndrome, Klinefelter syndrome and Bloom syndrome as well as immune deficiencies (HIV/AIDS, severe combined immune deficiency, Wiskott–Aldrich syndrome, common variable immune deficiency and organ transplantation). The frequency of PFs for CNS tumours in the cohort was 0.54%; it was 1.7% and 1.6%, respectively, for PFs of leukaemia and lymphoma. The most frequent PFs were organ transplantation (observed in 749 of the 67 274 members of the cohort − 1.11%), HIV/AIDS (0.36%), Down syndrome (0.3%), neurofibromatosis types 1 and 2 (0.16%) and other phacomatoses (0.29%). These percentages, though low, are greater than in the general population and their presence appears to be related to a slightly increased frequency and slightly decreased age at CT examinations, thus potentially confounding the association between radiation from CTs and risks of the aforementioned neoplasms.

During the study period, 27 CNS tumours, 25 leukaemia and 21 lymphoma were observed in the cohort; of these 7, 5 and 7, respectively, had a PF for CNS, leukaemia or lymphoma. In Table 5 of their paper, the authors show that adjustment for PFs reduced the excess relative risk estimates related to cumulative doses from CT scans (Table 1). This led them to conclude 'This study suggests that the indication for examinations, whether suspected cancer or PF management, should be considered to avoid overestimation of the cancer risks associated with CT scans'. Results shown in their Supplementary Table 6, however, focusing on the ERR/mGy among subjects with and without PF, challenge, in our opinion, this interpretation.

Indeed, risk estimates among subjects with no PF are similar to—although slightly higher than—the unadjusted risk estimates for brain tumours and lymphoma (see Table 1). This observation suggests that PFs are not, in fact, confounders of the association between cumulative organ radiation dose from CT and risk of these tumours, but rather possible effect modifiers. Though the authors conducted tests of homogeneity of risks between subjects with and without PFs, they were based on small numbers of subjects and hence the power to formally identify effect modification was very limited. For leukaemia, the ERR/mGy among subjects without PF are

Table 1. Number of cases (*N*) and ERR per mGy for tumours of the CNS, leukaemia and lymphoma, crude or adjusted for the presence of PFs and by patient's characteristics regarding presence of factors predisposing specifically to cancer at the site specified (PF)

	All cases (2-year exclusion period)			Subgroups			
		Unadjusted	Adjusted for PF	Without PF		With PF	
	N	ERR/mGy (95% CI)	ERR/mGy (95% CI)	*N*	ERR/mGy[a]	*N*	ERR/mGy[a]
CNS tumours	22	0.022 (−0.016; 0.061)	0.012 (−0.013; 0.037)	15	0.028	7	−0.005
Leukaemia	17	0.057 (−0.079; 0.193)	0.047 (−0.065; 0.159)	12	0.187	5	−0.012
Lymphoma	19	0.018 (−0.068; 0.104)	0.008 (−0.057; 0.073)	12	0.025	7	−0.005

Abbreviations: CNS = central nervous system; ERR = excess relative risks; PF = predisposing factor.
[a]Confidence intervals not provided.