ORIGINAL ARTICLE

Mortality study of chemical workers exposed to dioxins: follow-up 23 years after chemical plant closure

Ulf Manuwald,1,2 Marcial Velasco Garrido,2 Jürgen Berger,3 Alfred Manz,4 Xaver Baur1,2

ABSTRACT

Objectives To examine the long-term effects of dioxin-exposure, particularly with regard to cancer mortality, in a follow-up 23 years after closure of the chemical plant (Hamburg, Germany).

Methods The study comprised all persons (1191 men/398 women) employed in the plant on a full-time basis for a minimum of 3 months between 1952 and 1984 when the plant was closed down. Mortality follow-up was performed for the period from 1952 up to the reference date of 31 December 2007. Subjects entered the cohort at the date of their first employment in the plant. We calculated standardised mortality ratios (SMRs) using the population of Hamburg as reference.

Results The vital status could be determined for 96.5% of the study group (1145 men and 389 women). For men, there was an increase in overall mortality (ICD-9 1–999) (SMR = 1.14, 95% CI 1.06 to 1.23), all-cancer mortality (SMR = 1.37, 95% CI 1.21 to 1.56) and specific mortality from respiratory cancer (ICD-9 161, 162, 163) (SMR = 1.64, 95% CI 1.32 to 2.03), oesophageal cancer (ICD-9 150) (SMR = 2.56, 95% CI 1.27 to 4.57), rectum cancer (ICD-9 154) (SMR = 1.96, 95% CI 0.98 to 3.51), as well as diseases of the circulatory system (ICD-9 390–459) (SMR = 1.16, 95% CI 1.02 to 1.31). For women, there was an increase in breast cancer mortality (ICD-9 174) (SMR = 1.86, 95% CI 1.12 to 2.91).

Conclusions The results of this extended follow-up are consistent with those of previous analyses of the cohort and with those of other cohorts. Our findings support the carcinogenic effect of dioxin compounds.

INTRODUCTION

Dioxins are a group of chlorinated organic compounds with a core structure of two benzene rings joined by two oxygen atoms. The term ‘dioxins’ is often used to refer to complex mixtures of dioxin congeners and furans.

The most well known and studied is the dioxin compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD, TCDD), also known as chlorinated dibenzo [p,e] (1,4)-dioxin, tetrachlorodibenzo-p-dioxin. Dioxins can arise as by-products in the synthesis of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), a component of herbicides and insecticides and also of the defoliant ‘Agent Orange’ especially used in large scale during the Vietnam War.

2,3,7,8-TCDD was classified by the International Agency for Research on Cancer in 1997 as a group 1 carcinogen, which indicates that it is carcinogenic to humans. At that time, this decision was based on the evidence of an increased cancer mortality risk provided by several occupational cohorts. Ott and Zober1 reported increased cancer mortality (13 cancer deaths; standardised mortality ratio (SMR) = 1.97, 95% CI 1.05 to 3.56) among workers involved in the clean-up, repair and demolition activities after a reactor accident in a chemical plant 20 years earlier and who developed chloracne from exposure to 2,3,7,8-TCDD. Increased cancer mortality was also reported by Becker et al in another cohort of workers exposed to TCDD (77 deaths; SMR = 1.2, 95% CI 0.95 to 1.5). Similarly, Fingerhut et al4 found significantly increased cancer mortality in their study of workers with at least 1-year duration of exposure and at least 20 years of latency (114 cancer deaths; SMR = 1.5, 95% CI 1.2 to 1.8). Dutch workers with a high level of exposure to TCDD were also found to be at increased risk of dying from cancer (51 cancer deaths; SMR = 1.5, 95% CI 1.1 to 1.9).5

The workers at a chemical factory located in Hamburg, Germany, had been exposed to a considerable amount of primary substances, intermediate products and final herbicide and insecticide products during their manufacture between 1952 and 1984. For the various stages of production, contaminants included dioxins and furans in various concentrations, including 2,3,7,8-TCDD, but also other toxic agents, such as hexachlorocyclohexane (HCH) and benzene.6

Manz et al7 followed-up mortality 5 years after the closure of the plant and reported significantly increased cancer mortality among men (SMR = 1.24, 95% CI 1.00 to 1.52) in comparison...
with national mortality statistics for West Germany and in comparison with workers of the Hamburg gas supply company (SMR=1.39, 95% CI 1.10 to 1.75). Extended follow-ups have been published by Flesch-Janys et al\(^7\) and Becher et al\(^8\) confirming the initial findings. An updated follow-up 8 years after closure of the plant included 1189 men and showed increased overall mortality (413 deaths from all causes; SMR=1.15, 95% CI 1.05 to 1.27) as well as increased overall cancer mortality (124 cancer deaths; SMR=1.4, 95% CI 1.2 to 1.7) with significantly increased mortality for various specific cancers.\(^9\)

The objective of the current report was to analyse cancer mortality over the long term. The follow-up of the Hamburg chemical plant workers cohort was extended to 2007, that is, 23 years after closure of the plant. The number of deaths in the cohort had almost doubled in comparison with the last follow-up in 1992 and we anticipated gender-related analyses and analysis of exposure–response relationships to be possible from the enhanced statistical power.

**MATERIALS AND METHODS**

**Study group**

The study group included 1589 male and female workers, who were employed on the 1 January 1952 or later and for at least 3 months. Person-years for those included were counted from day 1 of their employment. The plant closed on 18 June 1984. Vital status was assessed by the reference date of 31 December 2007 (end of follow-up). Community inhabitant registries were queried to determine the vital status of cohort individuals. Workers whose vital status could not be determined on the reference date were excluded from the study.

The factory produced various herbicides and insecticides, including 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), the production of which started in 1952. Substantial contamination occurred from TCDD and higher chlorinated dioxins and furans, particularly from the production of 2,4,5-T and also from other product lines, established the year 1952 as the starting point for exposure to the relevant agents.\(^5\)

**Determination of the causes of death**

The causes of death in the study group were determined by an experienced physician (pathologist) from the death certificate and relatives, provided additional information

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**Reference group**

The mortality statistics of the populations of Hamburg and the Federal Republic of Germany (FRG West) (WHO data) were used to obtain expected numbers of causes of death for the period from 1 January 1955 onward (regional statistics Hamburg, northern Germany) and from 1 January 1952 onward (FRG from WHO). Since there were no significant differences in mortality rates between the total population (FRG West) and the population of Hamburg,\(^5\) we report the SMR obtained with the latter reference only.

Causes of death in official statistics were coded according to ICD-6 to ICD-10 and to a national classification\(^*\) used until 1967 in the official German mortality statistics. For comparison with the exposed cohort, causes of death were converted into ICD-9 diagnoses according to the method proposed by Vrijheid et al\(^11\) by creating groups of causes of death.

**Estimation of cumulative job exposure to TCDD**

Most of the workers changed their workplace within the plant several times during their employment history. The intensity of exposure to TCDD has been estimated retrospectively for the different workplaces in the plant in a previous analysis, based on dioxin analyses in blood or fat tissue samples.\(^6\) Furthermore, for each single worker, a complete work history was obtained from the company records. Total cumulative exposure for each individual was calculated as the sum of the cumulative exposures in each of the workplaces where the worker had been employed. For each workplace, cumulative exposure was calculated as the product of total time spent in a workplace and the workplace specific exposure estimated previously.\(^6\)

**Statistical analyses**

Gender-specific SMRs were calculated based on standard procedures (Breslow and Day\(^12\)). 95% CIs were calculated according to the Byar method, which is accurate even for small numbers of death.\(^12\)

To address exposure–response relationships, the cohort was divided according to exposure quartiles. We conducted exposure–response analysis stratified by gender for the following mortality categories with sufficient number of deaths: all causes (ICD-9 1–999), malignant neoplasms (ICD-9 140–208), malignant neoplasms of digestive organs and peritoneum (ICD-9 150–159), respiratory cancer (ICD-9 161, 162, 163), malignant neoplasm of female breast (ICD-9 174) and diseases of the circulatory system (ICD-9 390–459). In addition, we analysed potential risk differences around the cut-off of 200 parts per trillion (ppt). In Germany, this cut-off has been used as a convention in occupational disease compensation issues regarding dioxin-related cancer.\(^13\)

Cochran–Armitage trend tests were performed to evaluate exposure–response relationships between exposure quartiles. All data were encoded and digitally processed with strict confidentiality.

All calculations were performed with the spreadsheet program MS Office 2007 Excel®, and the Cochran–Armitage trend tests were performed with the Statistical Analysis System® (SAS V8.1).

**RESULTS**

The cohort characteristics of the follow-ups 1989, 1992 and 2007 are shown in table 1. On the chosen reference date of 31 December 2007, the vital status was determined for 96.1% of the study cohort. Vital status was unknown for 55 former workers.
mortality from suicide among men (SMR=1.7, 95% CI 1.17 to 2.46).

For women, we observed a lower-than-expected overall mortality (table 2). This could be mainly explained by a lower cardiovascular mortality among the female employees (58 deaths due to cardiovascular diseases, SMR=0.91, 95% CI 0.78 to 1.05). From 396 women, 65 died of cancer, and of them 19 died of breast cancer, resulting in an increased breast cancer mortality (ICD-9 174) (SMR=1.86, 95% CI 1.12 to 2.91).

Estimated cumulative job exposure to TCDD
The median cumulative job exposure for TCDD among men was 77.4 ppt and ranged from 0 to 16,514 ppt. Among women, the calculated TCDD exposure ranged from 0 to 15,195, with a median of 19.5 ppt. SMRs for cumulative TCDD job exposure quartiles are shown in table 3 for both men and women. The results did not show a clear exposure–response pattern, and no statistically significant trends for any of the causes of death were found neither for men nor for women.

In respect of the cut-off of 200 ppt TCDD, we observed that the SMR for overall cancer was increased both below and above this cut-off for men but only below the cut-off for women (table 5).

**DISCUSSION AND CONCLUSIONS**

Previous analyses of this cohort have been published before. The present follow-up extends the observation period by 15 years up to 2007, that is, 23 years after closure of the plant, with few employees lost to follow-up (a vital status known for 96.5% of the cohort). Compared with the previous follow-up in 1992, the numbers of deaths from malignant neoplasms (ICD-9 140–208) almost doubled from 124 to 226, which has enhanced the precision of SMR estimates.

Contamination with dioxins, including 2,3,7,8-TCDD, and furans occurred at various concentrations and production stages in the chemical plant. However, benzene, hexachlorocyclohexane and other toxic agents were also present as a result of the technical processes of production. In particular, during the processing of 1,2,4,5-tetrachlorobenzene to 2,4,5-trichlorophenol, the exposure to 2,3,7,8-TCDD was considerable. According to the Hamburg Environmental Authority, waste from the plant was contaminated with 2,3,7,8-TCDD at concentrations as high as 60 mg/kg.16

For the exposed cohort, the cause of death was determined solely from death certificates in 41% of cases, from medical records (including autopsy records) in 55% and from other sources (eg, insurance information) in 4% of cases.

Cause of death in the reference group was determined solely on information from death certificates. Generally, the physician who completes the death certificate is frequently not the treating physician and they are not always fully informed about the clinical history. This could lead to an overall underestimation of cancers, as well as to an overestimation of cardiovascular diseases in official statistics, resulting in a discrepancy between the statistically recorded cause of death and the actual cause.17 18

Such a differential classification for the exposed cohort and the reference population could lead to an overestimation of cancer-specific SMR in our study. However, a substantial misclassification in our analyses is unlikely since the causes of death among those exposed were determined according to the same procedure as in the reference group. In addition, we found a high degree of agreement (κ=0.74) in a random sample of records between the causes of death determined by a physician

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### Table 1  Cohort characteristics (follow-ups 1989, 1992 and 2007)

<table>
<thead>
<tr>
<th></th>
<th>Follow-up (1952–1989) n (%)</th>
<th>Follow-up (1952–1992) n (%)</th>
<th>Follow-up (1952–2007) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>1184 (100)</td>
<td>1189 (100)</td>
<td>1191 (100)</td>
</tr>
<tr>
<td>Vital status unknown</td>
<td>35 (3.0)</td>
<td>52 (4.4)</td>
<td>63 (5.3)</td>
</tr>
<tr>
<td>Vital status known</td>
<td>1149 (97.0)</td>
<td>1137 (95.6)</td>
<td>1128 (94.7)</td>
</tr>
<tr>
<td>Alive</td>
<td>838 (70.6)</td>
<td>763 (64.2)</td>
<td>450 (37.8)</td>
</tr>
<tr>
<td>Dead</td>
<td>313 (26.4)</td>
<td>414 (34.8)</td>
<td>695 (58.4)</td>
</tr>
<tr>
<td>Malignant neoplasms (140–208)</td>
<td>93 (7.9)</td>
<td>124 (10.4)</td>
<td>226 (19.0)</td>
</tr>
<tr>
<td>Diseases of circulatory system (390–459)</td>
<td>NA</td>
<td>157 (13.2)</td>
<td>251 (21.1)</td>
</tr>
<tr>
<td>External causes (800–999)</td>
<td>43 (3.6)</td>
<td>56 (4.7)</td>
<td>63 (5.3)</td>
</tr>
<tr>
<td>Other causes</td>
<td>NA</td>
<td>77 (6.5)</td>
<td>142 (11.9)</td>
</tr>
<tr>
<td>Cause of death unknown</td>
<td>5 (0.4)</td>
<td>13 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>

**NA,** not available.

(46 men and nine women); of these, 23 (42%) had worked for 1 year or less and the remaining 32 (58%) for more than 1 year. In contrast, 24% of the workers with known vital status had worked for 1 year or less and 76% for more than 1 year. Workers with unknown vital status had been employed in the plant for an average of 3.87 years compared with 6.89 years of employment for those persons whose vital status was known by the end of follow-up. Thus, the difference between the 55 persons lost to follow-up and the rest of the study cohort involves shorter periods of employment.

**Total mortality and disease-specific mortality**

The most frequent causes of death among cohort members were diseases of the circulatory system (ICD-9 390–459), accounting for 35.5% of all deaths. Respiratory cancers (ICD-9 160–169) accounted for 10.9% and digestive cancers (ICD-9 150–159) for 8.3% of all deaths.

Table 2 shows gender-specific age-SMRs obtained with the population of Hamburg as a reference.

For men, all-cause mortality was increased (SMR=1.14, 95% CI 1.06 to 1.25). This was mainly due to the increase in mortality from cancers and cardiovascular diseases. Several types of cancer contributed to the higher cancer mortality. The strongest mortality increases were observed for oesophageal cancer (ICD-9 150) (SMR=2.56, 95% CI 1.27 to 4.57) and for laryngeal cancer (ICD-9 161) (SMR=3.75, 95% CI 1.37 to 8.16).

The SMRs for cancer of the anus and rectum (ICD-9 154) (SMR=1.96, 95% CI 0.98 to 3.51), bladder cancer (ICD-9 188) (SMR=1.83, 95% CI 0.91 to 3.28) and kidney cancer (ICD-9 189) (SMR=2.00, 95% CI 0.80 to 4.12) were also increased. Besides increased cancer mortality, there was a significant increase in mortality from suicide among men (SMR=1.7, 95% CI 1.17 to 2.46).
with access to additional clinical information and by a professional coder based solely on death certificates. The physician classified 75 deaths as cancers, of which eight were coded as cardiovascular and four to other causes by the professional coder. Of the 64 cases classified as cancers by the professional coder, one was assigned to other causes by the physician. In the cohort, for example, those in production areas, were exposed to high or even extremely high dioxin concentrations, whereas others, such as office workers, to very low TCDD concentrations. The actual load of carcinogenic substances for the different jobs in the chemical plant is not known since neither ambient nor biological monitoring was performed during the production processes. The concentrations of toxic substances were estimated using pharmacokinetic models based on individual personal sampling or TCDD measurements in blood fat levels.8 The SMRs for all causes (ICD-9 0–999) and all malignant neoplasms (ICD-9 140–208) differed markedly for the group of men for whom the TCDD burden had been actually measured in biological samples except malignant neoplasm (ICD-9 189–208) differed markedly for the group of men for whom the TCDD burden had been actually measured in biological samples except malignant neoplasm of lymphatic and haematopoietic tissue.

The observed SMRs for neoplasms in the present follow-up may, however, underestimate the real situation because the cohort was not homogeneously exposed. Some subjects of the dioxin cohort, for example, those in production areas, were exposed to high or even extremely high dioxin concentrations, whereas others, such as office workers, to very low TCDD concentrations. The actual load of carcinogenic substances for the different jobs in the chemical plant is not known since neither ambient nor biological monitoring was performed during the production processes. The concentrations of toxic substances were estimated using pharmacokinetic models based on individual personal sampling or TCDD measurements in blood fat levels.8 The SMRs for all causes (ICD-9 0–999) and all malignant neoplasms (ICD-9 140–208) differed markedly for the group of men for whom the TCDD burden had been actually measured in biological samples except malignant neoplasm of lymphatic and haematopoietic tissue.
### Table 3: Comparison by TCDD levels. Quartile of estimated cumulative job exposure (TCDD based on blood fat) and SMR

<table>
<thead>
<tr>
<th>Quartile</th>
<th>TCDD (ppt) based on blood fat</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I &gt;0</td>
<td>II ≥13.1</td>
<td>III ≥27.6</td>
</tr>
<tr>
<td></td>
<td>to &lt;13.1</td>
<td>to &lt;7.4</td>
<td>to &lt;33.5</td>
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<tr>
<td></td>
<td>287</td>
<td>287</td>
<td>284</td>
</tr>
<tr>
<td>Cochran-Armitage trend test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>I II III IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.28 (1.10)</td>
<td>1.17 (1.01)</td>
<td>1.02 (0.87)</td>
</tr>
<tr>
<td></td>
<td>to 1.48</td>
<td>to 1.36</td>
<td>to 1.19</td>
</tr>
<tr>
<td></td>
<td>38/41.1</td>
<td>45/38.0</td>
<td>49/57.6</td>
</tr>
<tr>
<td></td>
<td>0.92 (0.65)</td>
<td>1.18 (0.86)</td>
<td>0.85 (0.63)</td>
</tr>
<tr>
<td></td>
<td>to 1.27</td>
<td>to 1.58</td>
<td>to 1.12</td>
</tr>
<tr>
<td></td>
<td>15/12.4</td>
<td>16/11.3</td>
<td>19/16.0</td>
</tr>
<tr>
<td></td>
<td>1.21 (0.70)</td>
<td>1.41 (0.84)</td>
<td>1.19 (0.74)</td>
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<td></td>
<td>to 2.03</td>
<td>to 2.39</td>
<td>to 1.90</td>
</tr>
<tr>
<td></td>
<td>1.18 (0.86)</td>
<td>1.41 (0.84)</td>
<td>1.19 (0.74)</td>
</tr>
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<td></td>
<td>to 2.39</td>
<td>to 1.90</td>
<td>1.58</td>
</tr>
<tr>
<td>SMR (95% CI)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.92 (0.65)</td>
<td>1.18 (0.86)</td>
<td>0.85 (0.63)</td>
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<tr>
<td></td>
<td>to 1.27</td>
<td>to 1.58</td>
<td>to 1.12</td>
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<td></td>
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<td>16/11.3</td>
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<td>to 1.90</td>
<td>1.58</td>
</tr>
</tbody>
</table>

SMR, standardised mortality ratio.
indicating that the group of workers with measured TCDD concentrations is not representative of the rest of the cohort (ie, some degree of differential selection of persons for blood sampling is present). Since the estimates of the workplace exposure were derived from these TCDD measurements, caution is in the interpretation of the analysis regarding the exposure—response relationship is warranted.

We observed a statistically significant excess mortality from all cancers in both men and women. This result is consistent with previous analysis of this cohort and with reports from other occupational cohorts. Specifically, we found an increased mortality from female breast cancer, with an SMR of 1.86 (95% CI 1.12 to 2.91), which is a more robust estimate than the one observed in the previous follow-up (SMR = 1.23, 95% CI 0.87 to 1.55). Our results are also consistent with previous analysis of this cohort and with reports from other occupational cohorts.

For respiratory cancer (ICD-9 161, 162, 163), there was a higher mortality in men but not in women. With our data, we could not control for smoking; however, the prevalence of smoking had been estimated previously for a subgroup of the cohort and it did not differ from that of the general population. In addition, we found low mortality from non-malignant respiratory diseases (see table 2), suggesting that smoking is not confounding our results relevantly. Increased respiratory cancer mortality has been also described in other occupational cohorts, although in the Dutch cohort the excess could not be explained from the estimated TCDD levels. We also could not identify a clear exposure—response relationship using estimated TCDD in our analysis.

The observed increased mortality due to pleural cancer (SMR = 5.66, 95% CI 1.67 to 6.94) is probably attributable to asbestos exposure in some areas of the plant. We also found an increased mortality of oesophageal cancer, rectum cancer and laryngeal cancer, which almost double that of the Hamburg population. Excessive mortality from rectum cancer has been also reported previously by other authors. Recently, Boers et al. calculated significant increased SMR for bladder cancer (SMR = 3.72, observed/expected (O/E) 9.2/2.42) and kidney cancer (SMR = 3.72; O/E 8/2.17). Our results are also consistent with these findings.

In general, the relationship of dioxin with different types of cancer concurs with the postulate of dioxins being a non-specific cancer promoter.

For women, we found a decreased overall mortality and decreased mortality from cardiovascular diseases (SMR = 0.74, 95% CI 0.74 to 0.94), which could be an indication of some degree of healthy worker effect, a frequent problem in occupational epidemiology.

Interestingly, among men, we found a significantly increased number of deaths from external causes (SMR = 1.50, 95% CI 1.14 to 1.94) and, specifically, suicides (SMR = 1.70, 95% CI 1.17 to 2.46), although no suicide type predominated. A notorious tendency of dioxin-exposed workers to commit suicide has been reported before. In a cross-sectional survey of emotional complaints and deficits carried out among the cohort survivors in 1993, a significantly increased risk of suicidal thoughts (OR = 2.78, 95% CI 1.26 to 6.15) and depressiveness in the Hamilton Depression Scale (OR = 3.70, 95% CI 1.39 to 9.62) (both adjusted among others for age, alcohol consumption and educational level) was observed. It is not unlikely that some suicides may have occurred in association with terminal malignant disease.

In summary, our results confirm and extend the observations of the previous follow-ups and support a general carcinogenic risk associated with exposure to dioxin compounds. The longer duration of the follow-up has increased statistical power. It cannot be ruled out, however, that concomitant toxic agents such as β-hexachlorocyclohexane, benzene and asbestos also acted as cofactors in the chemical plant under study.

Our findings do not indicate a safe level of dioxin (ie, low TCDD exposure values do not exclude an increased cancer risk) nor an exposure—response relationship on the basis of the available exposure assessment in the investigated cohort.

A subsequent follow-up of the Hamburg dioxin cohort will further increase the statistical power of our SMR analyses. There is a need, among others, to evaluate whether the observed trend of cancer mortality will continue in future.

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Contributors AM and XB conceived the idea. UM performed the calculations and assisted in the analysis. UM, MVG and XB wrote the first draft of the paper. All authors critically analysed results, interpreted the data, read, critically revised and approved the manuscript.

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Competing interests None.

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