Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial

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ABSTRACT
Background ITALUNG is contributing to the European evaluation of low-dose CT (LDCT) screening for lung cancer (LC).
Methods Eligible subjects aged 55–69 years, smokers or ex-smokers (at least 20 pack-years in the last 10 years), were randomised to receive an annual invitation for LDCT screening for 4 years (active group) or to usual care (control group). All participants were followed up for vital status and cause of death (at the end of 2014) and LC incidence (at the end of 2013). Pathological and clinical information was collected from the Tuscan Cancer Registry data.
Results 1613 subjects were randomly assigned to the active group and 1593 to the control group. At the end of the follow-up period 67 LC cases were diagnosed in the active group and 71 in the control group (rate ratio (RR)=0.93; 95% CI 0.67 to 1.30). A greater proportion of stage I LC was observed in the active group (36% vs 11%, p<0.001). Non-significant reductions of 17% (RR=0.83; 95% CI 0.67 to 1.03) for overall mortality and 30% (RR=0.70; 95% CI 0.47 to 1.03) for LC-specific mortality were estimated.
Conclusions Despite the lack of statistical significance, the ITALUNG trial outcomes suggest that LDCT screening could reduce LC and overall mortality. Moreover, the comparison of the number of LC cases diagnosed in the two groups does not show overdiagnosis after an adequate follow-up period. A pooled analysis of all European screening trials is advocated to assess the benefit-to-harm ratio of LDCT screening and its implementation in public health settings.

Trial registration number Results, NCT02777996.

BACKGROUND
Lung cancer (LC) is the leading cause of cancer deaths in men and the third in women in Italy, with an increasing incidence and mortality trend among women. Over 33 000 LC deaths occurred in 2012 and 41 000 LC diagnoses were estimated in 2015.5 Although slightly improving, the 5-year Cancer Registry-based LC survival rate in Italy is still only 14%.5 Both the LC incidence and mortality rates are decreasing among men as a consequence of the reduction in smoking. However, ageing of the Italian population will result in a substantial stability in the absolute number of LC deaths.5 New tobacco control policies have been implemented in Italy and the promotion of smoking cessation strategies is considered to be the leading primary prevention strategy to reduce smoking-attributable LC deaths.6

Screening for LC with low-dose CT (LDCT) in the National Lung Screening Trial (NLST) reduced LC mortality by 20%,3 and the guidelines for screening for LC were rapidly updated so that LDCT screening is currently recommended for high-risk subjects in the USA.6 Conversely, public health guidelines in Europe do not recommend screening for LC since the evidence of its benefits and harms has not been considered sufficient.7

The ITALUNG LC screening trial was launched in 2004 in Tuscany, an Italian administrative region, with the aim of contributing to the European evaluation of the efficacy of LDCT screening for reducing LC-specific and overall mortality and an assessment of the benefit-to-harm ratio.

METHODS
ITALUNG is a randomised controlled trial (RCT) of screening for LC, comparing LDCT to usual...
Lung cancer
care, carried out in three Tuscan screening centres (Florence, Pisa and Pistoia). The study design and criteria for a positive test were previously reported as the major indicators of screening performance in the active group. A flow chart of the management of non-calcified solid, part-solid and non-solid nodules detected at baseline or repeat LDCT screening is shown in the online supplementary appendix (section 1).

Subjects recruited from the patient lists of 269 general practitioners were sent a letter with a standardised questionnaire which they were requested to return by post giving consent to be randomised. Subjects were eligible if they were aged 55–69 years with a smoking history of at least 20 pack-years in the last 10 years (former smokers who had quit more than 10 years ago were excluded). As the enrolment was based on the year of birth, a small percentage of subjects were 54 years old at the date of randomisation (but they became 55 during that calendar year); in the same way, subjects aged 69 years at randomisation became older during the calendar year. Other exclusion criteria were a history of previous cancer other than non-melanoma skin cancer and general conditions precluding thoracic surgery. Eligible subjects were centrally randomised by a software procedure into an active group receiving an annual invitation to LDCT screening for 4 years and a control group receiving usual care. Subjects in the active group were given a clinical standardised interview. Control group subjects received a letter communicating their allocation. Both groups received an invitation to a free smoking cessation programme.

Statistical analysis
The study’s primary endpoint was the comparison of LC mortality between the active and control groups using the rate ratio (RR) with 95% CI. Secondary analyses compared the rate of death from any cause, the rate of death from any cause except LC and the incidence of LC in the two groups.

Power calculation was made assuming pooling of mortality data with other European trials, among which the NELSON trial is the largest. Assuming a 25% reduction in LC mortality among screened subjects after 10 years of follow-up, the required sample size for a power of 80% was calculated to be between 15 200 and 18 700 subjects (depending on the eligibility criteria of the participants). Subjects who withdrew from the screening process at any time after randomisation were considered as dropouts but, in accordance with the intention-to-treat principle, were included in the active group.

All participants were followed up for vital status and cause of death until 31 December 2014. Follow-up for vital status was performed via the population mortality registries and included a check for residential status. An independent committee reviewed and revised the causes of death in a blinded fashion using a specific algorithm presented in the online supplementary appendix (section 2).

All participants were followed up for the incidence of LC until 31 December 2013 through links to the Tuscan Cancer Registry. In cases of multiple LC diagnoses in the same subject, only the first was considered. All LC patients were classified as either treated with surgery or not, and disease stage was determined on the basis of histology reports (pTNM) or clinical information when histology reports were not available (ie, all non-resected patients and five resected patients with missing histology reports) according to the 7th edition of the TNM classification. Histological characteristics were coded according to the International Classification of Disease for Oncology, 3rd edition (ICD-O-3). Morphological characterisation was cytology-based in cases in which neither core biopsy nor surgery were performed.

All active group subjects who were diagnosed with LC were classified as either screen-detected (diagnosis as a result of a screening test or a follow-up test in accordance with the protocol), clinically detected while in screening (diagnosis not as a result of screening but the subject had attended at least one screening test) or clinically detected among the unscreened (subjects who did not attend any screening test).

The person-years at risk were counted from the date of randomisation to the date of event (LC diagnosis or death) or to the date of censoring (migration or end of follow-up), whichever came first.

Major complications from invasive diagnostic procedures were monitored and compared between the two groups according to two indicators:

- a. mortality within 60 days after the surgical treatment, defined as the proportion of enrolled subjects who died within 60 days after surgical treatment;

- b. mortality within 60 days after most invasive diagnostic procedure (surgery, biopsy, bronchoscopy or fine needle aspiration cytology), defined as the proportion of enrolled subjects who died within 60 days after an invasive diagnostic procedure. For patients who did not undergo an invasive procedure, deaths were included if they occurred within 60 days after the diagnosis date.

In the survival analysis we included only study subjects diagnosed before or on 31 December 2013. The median follow-up time from the date of diagnosis was 1.2 years (Q1–Q3: 0.6–3.4). The 3-year LC survival was estimated using the Kaplan-Meier method and the difference between survival curves was tested using the log-rank test.

RESULTS
Figure 1 shows subject recruitment and outcomes (LC diagnosed, LC deaths and deaths from other causes) for the active and control groups at the end of the follow-up period. From 2004 to 2006, 71 232 invitation letters were sent to subjects aged 55–69 years resident in one of the three districts included in the study. The questionnaire was sent back to the screening centre by 17 055 responders, of whom 3206 were eligible to be randomised. Participants were randomly assigned to the active group who received annual LDCT screening for 4 years (n=1613) or to the control group who received usual care (n=1593).

Among subjects allocated to the active group, 1406 underwent the baseline LDCT scan. The 207 dropouts between randomisation and the baseline screening test were mainly due to refusal to undergo baseline LDCT after randomisation (79.2%). Overall, there was 81% adherence to the screening protocol across the four LDCT rounds (1302/1613), with both the 1258 subjects who attended all four LDCT rounds and the 44 subjects who attended fewer than four LDCT rounds due to LC diagnosis or death being considered as compliant with the protocol.

The demographic characteristics and smoking habits of the enrolled subjects by study group are presented in table 1. The distribution of subjects by age, sex and smoking habits (smoking status and pack-years) was well balanced between the two groups.

LC incidence
The median follow-up time for LC incidence was 8.5 years (Q1–Q3: 7.9–8.9). A total of 67 lung cancers (49.9 per 10 000 person-years) were diagnosed in the active group compared...
with 71 (53.7 per 10 000) in the control group (RR=0.93; 95% CI 0.67 to 1.30). Among the LC cases diagnosed in the active group, 38 (57%) were screen-detected, 25 (37%) were clinically detected in screened subjects and 4 (6%) were clinically detected in unscreened subjects (ie, those who refused screening immediately after randomisation).

Figure 2 shows the cumulative number of lung cancers diagnosed up until 31 December 2013 per study group. The excess of cases in the active group was 55% in the first 4 years (the screening period) whereas a 45% reduction was observed in the 5 years post-screening. The catch-up of the cumulative number of lung cancers took between 6 and 7 years from randomisation.

In table 2 the characteristics of the diagnosed lung cancers are presented per study group. About half of the patients in the active group were treated with surgery compared with a quarter in the control group (52% vs 28%, p=0.003). Similarly, a greater proportion of stage I cancers was observed in the active group than in the control group (36% vs 11%, p<0.001). The distribution by histotype showed a non-significant excess of adenocarcinoma in the active group (43% vs 30%, p=0.09) whereas the proportion of small cell carcinomas was 15% in both groups. The characteristics of LC diagnosed in the active group by modality of detection (screen-detected, clinically detected among screened and among unscreened) are reported in the online supplementary appendix (section 3).

Overall and LC-specific mortality
After a median follow-up of 9.3 years (Q1–Q3: 8.8–9.9), the active group showed a non-significant 17% reduction (RR=0.83; 95% CI 0.67 to 1.03; p=0.08) in overall mortality and a 30% reduction (RR=0.70; 95% CI 0.47 to 1.03; p=0.07) in LC-specific mortality compared with the control group (table 3). There were 154 deaths in the active group and 181 deaths in the control group, corresponding to rates of death from any cause of 105.1 and 127.0, respectively, per 10 000 person years. Among these, 43 deaths from LC (29.3 per 10 000 person-years) were observed in the active group compared with 60 (42.1 per 10 000) in the control group. The absolute rate difference (per 10 000) between the active and control groups was 21.9 for overall mortality and 12.8 for LC-specific mortality. Among subjects who died of LC in the active group, 17 (40%) were screen-detected, 23 (53%) were clinically detected in screened subjects and 3 (7%) were clinically detected in unscreened subjects.

Table 1 Characteristics of study participants (n=3206)

<table>
<thead>
<tr>
<th></th>
<th>Active group (n=1613)</th>
<th>Control group (n=1593)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre</td>
<td>Florence (795 (49%)</td>
<td>783 (49%)</td>
</tr>
<tr>
<td></td>
<td>Pisa (395 (25%)</td>
<td>392 (25%)</td>
</tr>
<tr>
<td></td>
<td>Pistoia (422 (26%)</td>
<td>418 (26%)</td>
</tr>
<tr>
<td>Age at entry (years)</td>
<td>&lt;55 (53 (3%)</td>
<td>64 (4%)</td>
</tr>
<tr>
<td></td>
<td>55–59 (687 (43%)</td>
<td>616 (39%)</td>
</tr>
<tr>
<td></td>
<td>60–64 (497 (31%)</td>
<td>526 (33%)</td>
</tr>
<tr>
<td></td>
<td>65–69 (371 (23%)</td>
<td>382 (24%)</td>
</tr>
<tr>
<td></td>
<td>&gt;69 (5 (0.3%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>Mean age at entry</td>
<td>60.9</td>
<td>60.7</td>
</tr>
<tr>
<td>Sex</td>
<td>Male (1035 (64%)</td>
<td>1039 (65%)</td>
</tr>
<tr>
<td></td>
<td>Female (578 (36%)</td>
<td>554 (35%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Current (1059 (66%)</td>
<td>1018 (64%)</td>
</tr>
<tr>
<td></td>
<td>Former (554 (34%)</td>
<td>575 (36%)</td>
</tr>
<tr>
<td>Median pack-years of smoking</td>
<td>40</td>
<td>38</td>
</tr>
</tbody>
</table>

Figure 1 Subject recruitment and outcome of the ITALUNG trial.

The lower overall mortality of the active group fell to a statistically non-significant 11% when deaths for LC were excluded (RR=0.89; p=0.38) (table 3). Although the outcomes of the study did not include cause-specific mortality, we observed a statistically significant reduction for cardiovascular mortality (RR=0.51; p=0.009).

Figure 3 shows the cumulative number of overall deaths and LC deaths by years from randomisation per group. Although overall mortality was quite similar in the two groups during the screening phase (RR=0.97; p=0.86), a significant 23% reduction was observed in the active group in the post-screening period (RR=0.77; p=0.045). There was a slight non-significant excess of LC-specific mortality in the active group during the screening period (RR=1.20; p=0.62) but, in the post-screening period, a significant 46% reduction (RR=0.54; p=0.01) was observed.

Adverse events
The death rates within 60 days after surgical treatment were 1.2 (2/1613) and 1.3 (2/1593) per 1000 in the active and control groups, respectively (p=0.99). Similarly, the death rates within 60 days after most invasive diagnostic procedure were almost the same in the two groups, 3.7 (6/1613) vs 3.8 (6/1593) per 1000, p=0.98 (adverse events are listed in section 4 of the online supplementary appendix). Although the two groups had a similar cumulative frequency of adverse events, those in the active group occurred sooner in time due to diagnostic anticipation. Indeed, two out of six deaths—defined as adverse events in the active group—occurred in screen-detected patients.

LC survival
In total, 99 deaths from any causes (96 from LC and 3 from other causes) were observed among 138 LC diagnoses by 31 December 2013. The 3-year LC survival was 44% and 25% for the active and control groups, respectively (p=0.07). In figure 4, LC survival curves shown by type of treatment (surgically

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**Table 2** Surgery, stage and histological type of lung cancers in the study groups (n=138)

<table>
<thead>
<tr>
<th></th>
<th>Active group (n=67)</th>
<th>Control group (n=71)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resected</td>
<td>35 (52%)</td>
<td>20 (28%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Not resected</td>
<td>32 (48%)</td>
<td>51 (72%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>24 (36%)</td>
<td>8 (11%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 (7%)</td>
<td>5 (7%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9 (13%)</td>
<td>8 (11%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>24 (36%)</td>
<td>35 (49%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (7%)</td>
<td>15 (21%)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Histological type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>29 (43%)</td>
<td>21 (30%)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>14 (21%)</td>
<td>17 (24%)</td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancers</td>
<td>10 (15%)</td>
<td>11 (15%)</td>
<td></td>
</tr>
<tr>
<td>Carcinoid</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Non-small cell carcinoma†</td>
<td>3 (4%)</td>
<td>5 (7%)</td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>9 (13%)</td>
<td>17 (24%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Pathological or clinical.
†This category includes six non-small cell carcinomas (not other specified) and two adenoquamous carcinomas.

**Table 3** Mortality rate (per 10 000 person-years) and rate ratios by group

<table>
<thead>
<tr>
<th></th>
<th>Active group</th>
<th>Control group</th>
<th>Rate ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years*</td>
<td>14 658</td>
<td>14 247</td>
<td>0.83 (0.67 to 1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Overall mortality rate</td>
<td>105.1 (n=154)</td>
<td>127.0 (n=181)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer mortality rate</td>
<td>29.3 (n=83)</td>
<td>42.1 (n=86)</td>
<td>0.70 (0.47 to 1.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>Overall mortality rate except lung cancer</td>
<td>75.7 (n=111)</td>
<td>84.9 (n=121)</td>
<td>0.89 (0.69 to 1.15)</td>
<td>0.38</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>15.0 (n=22)</td>
<td>29.5 (n=42)</td>
<td>0.51 (0.30 to 0.85)</td>
<td>0.009</td>
</tr>
<tr>
<td>Other causes</td>
<td>60.7 (n=89)</td>
<td>55.5 (n=79)</td>
<td>1.10 (0.81 to 1.48)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Follow-up at 31 December 2014.
resected/not resected) and study group indicate that there was no difference in 3-year survival between the two groups for patients treated with surgery (74% vs 67%, p=0.70). Similarly, survival in unresected patients was 7% and 8% in the active and control groups, respectively (p=0.50).

DISCUSSION
At 9 years of follow-up, non-significant reductions of 30% in LC-specific mortality (p=0.07) and 17% in overall mortality (p=0.08) were observed in the group screened with LDCT in comparison with the usual care control group. Despite the lack of statistical significance, we observed a consistent temporal trend. Indeed, the analysis by length of follow-up strengthened these results: no difference in mortality was observed during the screening phase (the 4 years following randomisation) whereas a significant reduction in both LC-specific (p=0.01) and overall mortality (p=0.045) was observed in the post-screening period.

Notably, the decrease in mortality observed in our study was larger than that reported in the NLST, in which decreases of 20% and 7% in LC-specific and overall mortality, respectively, were observed at 6.5 years of median follow-up. Besides the statistical uncertainty due to the different sample sizes of the NLST and ITALUNG studies, several factors must be considered in comparing their mortality data. First, the larger percentage decrease in LC mortality observed in the ITALUNG trial is probably explained by the longer follow-up, as shown from the trend of the mortality curves (the difference between the two groups became evident from the sixth year). Second, in the

Figure 3  Cumulative numbers of (A) overall deaths and (B) lung cancer deaths by year from randomisation per group. The number of deaths includes deaths that occurred from the date of randomisation through 31 December 2014. The grey area indicates the screening period.
ITALUNG trial, subjects enrolled in the control group were not invited to screening but received usual care, whereas in the NLST the control group underwent chest posterior-anterior (PA) radiography. The proportion of LC cases in the control groups diagnosed at an early stage and treated with surgery was noticeably higher in the NLST than in the ITALUNG trial (44% vs 28% had surgery and 31% vs 11% were diagnosed at an early stage in the NLST and ITALUNG trials, respectively) (see NLST online supplementary appendix1). Third, the eligible subjects enrolled can have different risk profiles for LC, as we have shown by comparing the risk profile and performance of ITALUNG with that of the NLST and the UK Lung Cancer Screening (UKLS) trial.13 14 The evaluation of risk profiles across studies is a further important motivation for the pooled analysis of LC screening trials. Fourth, it is important to note that only 40% of the LC deaths in the active group occurred in screen-detected LC cases, a proportion which was influenced by the length of the post-screening phase and which suggests that the effect of LDCT screening could have been even larger.

In the ITALUNG trial the distribution of LC stage differed strongly by group, with 36% and 11% of LC cases diagnosed at an early stage in the active and control groups, respectively. Of the LC cases in the active group, 52% were treated with surgery compared with only 28% in the control group (p=0.004). Survival analyses showed that the difference in LC survival between the two groups was entirely attributable to the different proportion of subjects treated with surgery (or to the different proportion of early stage cancers).

The LC incidence pattern in the ITALUNG trial confirmed the high sensitivity of LDCT screening. Indeed, during the screening phase we observed a 55% excess incidence in the active group followed by a 45% compensatory reduction in the following phase we observed a 55% excess incidence in the active group. The cumulative incidence curves of the NLST showed that catch-up had not been reached at 6.5 years of average follow-up, at which time 64.5 per 10 000 LC cases were diagnosed in the LDCT group in comparison with 57.2 in the PA chest radiography group—a 13% excess (RR=1.13; 95% CI 1.03 to 1.23).

After exclusion of LC deaths, the all-cause mortality in the active group decreased by 11%. However, an unexpected mortality reduction in cardiovascular diseases emerged which was statistically significant. This hinted at a possible contribution from LDCT screening or from the clinical encounter with the pulmonologist in determining better management of health conditions frequent in subjects at risk of or affected by smoking-related chronic diseases. In addition, smokers participating in the active arm had slightly higher smoking cessation rates than those in the control group (21% vs 18%, p=0.09).15 The specific impact of LDCT on the management of cardiovascular diseases should be assessed in the pooled analysis of LC screening trials.

The analysis of complications from invasive diagnostic procedures in the ITALUNG study did not support the hypothesis of important adverse effects of LC screening. Indeed, the frequency of adverse events was similar between the two groups, although differently allocated over time.

The ITALUNG study is representative of population-based LC care in central Italy. In an evaluation of the quality of cancer care carried out in Tuscany in 2004, the proportion of LC patients who underwent surgical treatment was 21%.16 Similarly, data from northern Italian cancer registries between 2003 and 2005 showed that surgery was carried out in 18% of cases and only 10% of LC cases were diagnosed at stage I.17

**CONCLUSIONS**

The ITALUNG RCT has, since its inception, been an active member of the USA-EU collaboration18 for the harmonisation of screening trials, with the ultimate aim of pooling results after the first outcome of each study has been published. In Europe, in addition to the ITALUNG trial, six other randomised LC screening trials are in progress.19 The Dutch-Belgian trial (NELSON),10 which is the largest European LC screening trial, has not yet published outcome data. DANTE,20 21 MILD22 and DLST23 24 have reported on their mortality data, which show no difference between the screening and control groups although, recently, pooled data from DANTE and MILD showed non-significant 11% and 17% reductions in overall and LC mortality, respectively.25 However, none of these published outcome studies alone, including the ITALUNG trial, has sufficient statistical power to detect a real benefit and, for specific analyses, as those assessing benefit for risk profile subgroups. A pooled analysis of all European trials including NELSON and the ongoing UKLS26 and LUSI27 RCTs is thus becoming a crucial step in assessing the expected benefit of LDCT screening in Europe.

Despite the lack of statistical significance, the ITALUNG trial outcomes suggest that LDCT screening could reduce LC and overall mortality. Together with the high false positive rate, overdiagnosis is the major potentially harmful effect of LDCT screening. Although further studies are necessary to confirm our results, the comparison of the number of LC cases diagnosed in the two groups in the ITALUNG study does not suggest overdiagnosis after an adequate follow-up period. This impression is supported by the results of the survival analysis, which show no difference if surgical treatment is taken into account.

The ITALUNG study has confirmed that LDCT screening, in conjunction with improvement of treatment strategies in early stage LC cases and effective national policies for smoking cessation, is an important tool for the reduction of deaths from LC.3 However, before implementation of LC screening programmes in Europe, there are still several critical issues that need to be addressed including optimisation of recruitment, especially for the identification of high-risk subjects (in which biomarkers may have their part to play) and definition of more efficient protocols for nodule management and the optimal screening interval.28 29 While waiting for the results of the NELSON and other European LC trials, it is anticipated that a combined rather than an individual study analysis will provide the following image:

**Figure 4** Lung cancer survival curves by surgery and group.
information necessary to support possible modification of public health guidelines in Europe.

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Contributors EP, ALP, LC, GP, FF, FMC, MM conceived the study design and information necessary to support possible modification of public health guidelines in Europe.

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