

# Latitude of the study place and age of the patient are associated with incidence of mediastinitis and microbiology in open-heart surgery: a systematic review and meta-analysis

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**Objective:** We aimed to summarize the pooled frequency of mediastinitis following open-heart surgery caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), and Gram-negative bacteria.

**Design:** This study was a systematic review and a meta-analysis of prospective and retrospective cohort studies.

**Materials and methods:** We searched the literature, and a total of 97 cohort studies were identified. Random-effect model was used to synthesize the results. Heterogeneity between studies was examined by subgroup and meta-regression analyses, considering study and patient-level variables. Small-study effect was evaluated.

**Results:** Substantial heterogeneity was present. The estimated incidence of mediastinitis evaluated from 97 studies was 1.58% (95% confidence intervals [CI] 1.42, 1.75) and that of Gram-positive bacteria, Gram-negative bacteria, and MRSA bacteria evaluated from 63 studies was 0.90% (95% CI 0.81, 1.21), 0.24% (95% CI 0.18, 0.32), and 0.08% (95% CI 0.05, 0.12), respectively. A meta-regression pinpointed negative association between the frequency of mediastinitis and latitude of study place and positive association between the frequency of mediastinitis and the age of the patient at operation. Multivariate meta-regression showed that prospective cohort design and age of the patients and latitude of study place together or in combination accounted for 17% of heterogeneity for end point frequency of mediastinitis, 16.3% for Gram-positive bacteria, 14.7% for Gram-negative bacteria, and 23.3% for MRSA bacteria.

**Conclusion:** Evidence from this study suggests the importance of latitude of study place and advanced age as risk factors of mediastinitis. Latitude is a marker of thermally regulated bacterial virulence and other local surgical practice. There is concern of increasing risk of mediastinitis and of MRSA in elderly patients undergoing sternotomy.

**Keywords:** mediastinitis, sternotomy, meta-analysis

## Introduction

The reported incidence of mediastinitis after coronary artery bypass grafting (CABG) is 0.4%–4%.<sup>1</sup> Mediastinitis is associated with increased morbidity, mortality, and cost.

The etiology and pathophysiology of mediastinitis are complex and multifactorial. Also, mediastinitis carries an excess of long-term risk of mortality over 10 years of follow-up.<sup>1,2</sup>

The variability of incidence of mediastinitis in the literature is due to different study designs, population of patients, surgical cardiac procedures, and geographical area of

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the world with climate and latitude differences. We know that the latitude where the study took place is an important marker for variation in rainfall, humidity, temperature, and environmental mycobacteria that may alter the natural immunity and other factors. Latitude is associated with intensity and duration of sun exposure. Also, ambient temperature and latitude are strongly correlated.<sup>3</sup> Previous studies have used latitude of study site as proxy for ambient temperature and environmental mycobacteria.<sup>4,5</sup> We used the same method to assess the etiological role of ambient temperature and mycobacteria on the incidence and microbiology of *Helicobacter pylori* in a systematic review combined with meta-analysis of the literature.<sup>6</sup> This systematic review considered worldwide studies of incidence and microbiology of mediastinitis after open-heart surgery.

## Materials and methods

### Literature search

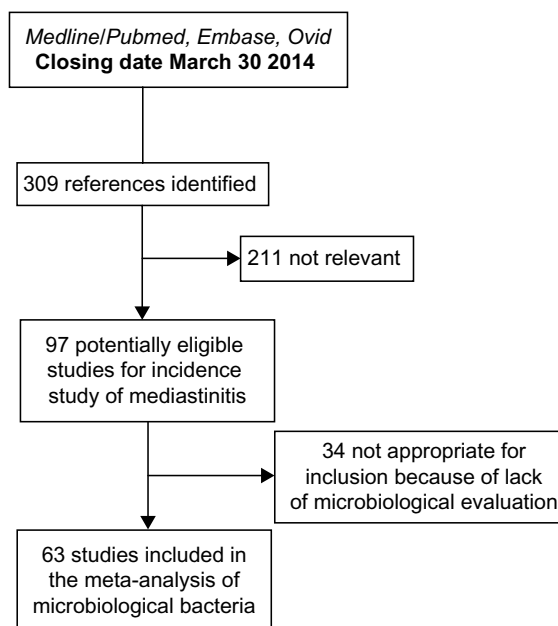
A qualified medical librarian of Medical Library, Oslo University Hospital, was consulted. We searched the Cochrane Central Register of Controlled Trials (1970–2014), Medline/PubMed (1966–2014), and Embase (1980–2014) databases. We used a combination of keywords and details of the search procedure as shown in the [Supplementary materials](#). We used similar strategies to identify previously published meta-analyses and reviews. In addition, we manually searched conference proceedings and textbooks, screened reference lists of all papers, and contacted investigators, experts, and translators. The last update for research was done on August 8, 2014. No limitation on language was considered (Figure 1).

### Study selection

We included prospective and retrospective studies on patients with open-heart surgery coronary artery bypass graft (CABG and valve replacement). Two reviewers independently evaluated reports for eligibility criteria defined as cohort of open-heart surgery patients operated in different centers of the world. Finally, 97 cohorts were considered eligible for the incidence study<sup>1,7–102</sup> and 63 of them were considered for microbiological incidence of Gram-positive cocci and Gram-negative bacilli and fungi.

### Quality assessment of the cohort studies: the component approach

Unfortunately, there is no agreed “gold standard” appraisal tool for evaluating quality in observational epidemiologic studies, and there are many tools from which to choose. For the purpose



**Figure 1** A flowchart of the literature searches for the systematic review of studies on the incidence of mediastinitis.

of critically appraising cohort studies, we used a checklist based on recommendations by Elwood,<sup>103</sup> including: a) methods for selecting study participant; b) directionality of the cohort, prospective versus retrospective; and c) enough power to catch the true incidence. The poor reporting on important methodological details may be due to the fact that most papers were published before the STROBE statements.<sup>104</sup> Sanderson et al<sup>105</sup> evaluated a large number of tools for assessing quality of observational epidemiological studies, recommending a simple checklist, including a small number of key domains being specific to the study design under consideration rather than a scale. Scales resulting in numerical summary of quality scores might look simple to use, but such an approach can introduce a bias when assessing study quality.<sup>106</sup>

### Data abstraction

Data regarding publication status, study design, patient-related characteristics, outcome methods, and results and funding were extracted in duplicate on a standardized form according to an a priori protocol. Authors were contacted for additional data and corrections. Disagreements were resolved by discussion with a third reviewer and subsequent consensus. Patient-related variables were considered in the protocol and included mean age of the cohort, frequency of female sex, and frequency of CABG surgery. The study-level variables included the nature of the cohort, prospective versus retrospective; latitude and longitude of the place of the study, year of publication, and the presence of adequate

power. The adequate power was based on the total incidence of deep sternal wound infection (DSWI).

Of the 97 studies, the observed median incidence was 1.5% and the lower and higher quartile were 0.70% and 2.3%, respectively. Considering the median of 1.5% and accepting a precision of 0.8% (half the interquartile range), we will need a cohort of at least 887 patients to have a 95% probability to catch this incidence.

## End points considered

The primary end point was the incidence of mediastinitis infection. The diagnosis of post sternotomy mediastinitis was based on the criteria established by the Centres for Disease Control and Prevention. We know that according to Centres for Disease Control and Prevention, surgical site infections can be classified into three categories: superficial incisional sternum superficial infections (SSIs; involving only skin and subcutaneous tissues), deep incisional SSIs (involving deep soft tissue), and organ/space SSIs (involving any part of the body other than the incision itself), which is opened or manipulated during the operative procedure. The definition of mediastinitis must meet at least one of the following criteria: 1) positive bacterial culture from the mediastinal space; 2) evidence of mediastinitis during surgery or histology; or 3) one of the following: fever ( $>38^{\circ}\text{C}$ ), chest pain, sternal instability, purulent discharge from the mediastinal area, organisms cultured from blood or from discharge of the mediastinal area, or mediastinal widening in radiology.

Unfortunately, in the literature, various terms for chest SSIs have been used, including sternal infection, deep sternal infection, and major infection. The inconsistent definitions could create misclassification of mediastinitis.

Secondary end points were the incidence of different microorganisms recovered in mediastinitis secondary to cardiovascular surgery. They included: 1) Gram-positive cocci (*Staphylococcus aureus* including methicillin-resistant *S. aureus* [MRSA], *Staphylococcus epidermis*, and *Enterococcus* spp.); 2) Gram-negative bacilli (*Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., and other *Enterobacteriaceae* and *Pseudomonas* spp.); 3) fungi (*Candida albicans* and others); and 4) polymicrobial mediastinitis (mixed Gram-positive and Gram-negative organisms account for  $>10\%$ ). Other microorganisms were occasionally reported.

## Quantitative data synthesis

### Statistical pooling

Random-effects meta-analysis of single proportions was considered to estimate a cumulative incidence. The

DerSimonian–Laird estimate<sup>107</sup> is used in the random-effects model. To obtain summary measures, we used random-effects model due to the large heterogeneity of the results. To pool the incidence measures, logit transformation and sometimes logarithm transformation were initially performed to handle the distribution asymmetry. Sometimes, we considered the Freeman-Tukey double arcsine transformation of the proportions to calculate an overall pooled proportion and to stabilize the variance.<sup>108</sup> These incidences were weighted by the inverse variance. When using the logit transformation, a continuity correction was applied if any studies had a zero cell count. By default, 0.5 is added to all cell frequencies of studies with a zero cell count. For individual studies, the Clopper-Pearson confidence interval was estimated.<sup>109</sup>

### Sources of heterogeneity, evaluation, and quantification

Statistical heterogeneity among studies was assessed with Cochran's Q test. The magnitude of heterogeneity was evaluated by the  $I^2$  statistics, which describes the proportion of total variation due to heterogeneity rather than chance.<sup>110</sup> In order to investigate possible sources of heterogeneity, two different methods were used: subgroup analyses and meta-regression. We stratified our data according to the following study characteristics: nature of the cohort, prospective versus retrospective, and presence of a priori power estimation for the study.

A random-effects model was used to combine subgroups with separate estimate of  $\tau^2$ .<sup>110</sup> After doing the subgroup analyses, we ran a random-effect meta-regression analysis, where the outcome variable was the transformed observed incidence from every study, indicating effect and study-level and patient-level characteristics (covariates). This random-effect regression model was done to enable exploration of the source of heterogeneity in the association between incidence of DWSI and covariates. The mixed model is an extension of the random-effect model. In this model, some heterogeneity is explained by moderators (covariates) and the rest by the random-effect term.

### Publication bias or small-study effect

In order to assess potential publication bias or small-study effect, we used the funnel plot, which is a good visual evaluation of sampling bias or small-study effect.

### Begg and Mazumdar rank correlation test

Begg and Mazumdar<sup>111</sup> suggested a test statistics based on rank correlation between standardized outcome estimates and

variance estimates of estimated outcome effect. Kendall's tau is used as a correlation measure. The test statistics follows a standard normal distribution.

### Egger's test of asymmetry

Another test of asymmetry (Egger's test)<sup>112</sup> applied on the funnel plot was performed. The test statistics is based on a weighted linear regression of the treatment effect on its standard error. The test statistics follows a normal distribution with number of studies -2 as degrees of freedom. Nowadays, Egger's test is mostly seen as a test of small-study effects.

### Detection and correction for publication bias/small-study effect using the trim and fill method

Publication bias is a serious issue, as it may lead to biased estimates, which appears to be precise. A popular method for detecting and adjusting bias is the trim and fill method.<sup>113</sup> When there is substantial heterogeneity, the trim and fill method is inappropriate to control for publication bias.<sup>114</sup>

### Power considerations in meta-analysis and meta-regression

The test of funnel plot asymmetry and meta-regression analysis can be used only when at least ten studies are included in the meta-analysis because of power limitations. As underlined by Borenstein et al<sup>110</sup> under the fixed model, the number of subjects in the studies and the effect size we need to pinpoint determine the power of the meta-analysis. Under the random-effect model, power is a function of not only the total number of subjects but also the number of studies, the effect size, and the variance between studies (heterogeneity).

For power consideration, we used a minimum of ten studies per covariate in a multivariate model of meta-regression. On the other hand, it is well known that aggregate variables (patient-related variables) are subject to ecological fallacy and must be considered only as hypothesis generating.

All statistical analyses were performed using the R package meta<sup>115</sup> and Stata 13.0.<sup>116</sup> We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for meta-analyses and systematic reviews of observational studies in the present report.<sup>117</sup>

## Results

### Trial flow

After identifying 309 references, 211 were excluded due to irrelevant content and duplicate publications, leaving 97 potentially eligible studies for incidence of mediastinitis. From these 97 eligible studies, 63 studies had microbiological

evaluation. Finally, 97 studies were included in our systematic review of incidence and 63 for microbiological specific bacteria (Figure 1).

### Study characteristics

The study characteristics considered were the place and latitude of the study, the year of publication, the mean age of the study population, frequency of female patients, frequency of isolated CABG, the prospective or retrospective nature of the cohort design, and the adequacy of power of the study.

### End point total incidence of DSWI or mediastinitis

A total of 1,420,845 patients were included in the 97 studies, and the number of patients with DSWI or mediastinitis was 13,662. The mean age was 62.24 years (n=61 studies) with a range from 51 years to 67.9 years. The frequency of female patients was 28.2% with a range from 1% to 75% (n=68 studies). Mean frequency of CABG was 81.1% (n=61 studies) with a range from 36.6% to 100%. For the study-level characteristics, all the studies had a cohort design with 59 prospective and 48 retrospective. Of the total 97 (85.7%) studies, 84 were adequately powered.

### End point bacteriology (incidence of microorganisms)

Only 63 of 97 studies have performed microbiological analysis and reported their results. Considering these studies, the number of patients included was 306,440 and the number of microorganisms (bacteria and fungi) was 3,724. The

**Table 1** Incidence of microorganisms recovered in mediastinitis secondary to cardiothoracic surgery with frequency in 63 cohort studies

Gram-positive cocci (n=2,958)
<i>Staphylococcus aureus</i> (n=1,397), including MRSA (n=343)
<i>Staphylococcus epidermis</i> (n=1057)
<i>Enterococcus</i> spp. (n=168)
<i>Streptococcus</i> spp. (n=24)
Gram-negative bacilli (n=733)
<i>Esherichia coli</i> (n=101)
<i>Enterobacter</i> spp. (n=142)
<i>Klebsiella</i> spp. (n=105)
<i>Proteus</i> spp. (n=19)
Other <i>Enterobacteriaceae</i> (n=52)
<i>Pseudomonas</i> spp. (n=117)
Fungi (n=33)
Other bacteria occasionally reported (n=509)

**Note:** Total number of microorganisms (bacteria + fungi) is 3,724 in 306,440 patients.

**Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus*.

total number of Gram-positive cocci was  $n=2,958$  (77.3%), including 343 MRSA microorganisms. Gram-negative bacilli represented 733 microorganisms, and the number of fungi infections was 33 (Table 1).

## Quantitative data synthesis

### End point incidence of DSWI (mediastinitis) in 97 studies worldwide

The summarized pooled estimate incidence of DSWI in the 97 studies using the random-effect model was 0.0158 (95% CI 0.0142–0.0175) with a substantial heterogeneity (Tables 2 and 3).

The funnel plot in Figure 2 visually showed evidence of bias and small-study effect. This was verified using Begg and Mazumdar rank correlation test and confirmed by the Egger's test, which had a  $P$ -value of 0.001 accepting the null hypothesis of small-study effect. Because of substantial heterogeneity, we did not correct for selection bias considering the trim and fill simulation method.

The presence of heterogeneity led us to an investigation of its origin. A stratification analysis on the prospective versus retrospective nature of the cohorts, the adequacy of powered studies versus power-deficient studies, and the median latitude of the place of the studies showed a significant difference between subgroups. We extended the analyses with a meta-regression model taking into account moderator variables such as mean age, frequency of CABG in the total open-heart surgery, frequency of female patients, and latitude. One important study-level variable identified was latitude (Figure 3) with decreasing incidence of mediastinitis with increasing latitude. There was an increasing incidence of DSWI with the increasing age of patient at sternotomy (Figure 4).

**Table 2** Estimate of incidence of mediastinitis with stratification on prospective nature and power of the cohort and on latitude of the study place using the random-effect model

Subdivision	n	Incidence (95% CI)	$\tau^2$	$I^2$ (%)	$P$ -value <sup>a</sup>
All studies	97	0.0158 (0.0142–0.0175)	0.0039	97.8	
<b>Prospective cohort design</b>					
Yes	49	0.02 (0.016–0.024)	0.0075	97.3	<0.0001
No/Unclear	48	0.012 (0.010–0.015)	0.0019	95.7	
<b>Powered study</b>					
Yes	82	0.0146 (0.013–0.016)	0.0036	98	0.021
No	15	0.0274 (0.0158–0.015)	0.0225	93.1	
<b>Latitude over median 40.71</b>					
Yes	49	0.0126 (0.0112–0.014)	0.0016	96.4	0.0001
No	48	0.0199 (0.0162–0.024)	0.009	97.7	

**Note:** <sup>a</sup>Test for subgroup differences using the random-effect model between groups with  $Q$  statistics,  $df=1$ , and  $P$ -value.

**Abbreviations:** CI, confidence interval;  $\tau^2$ , interstudy variability;  $df$ , degree of freedom.

**Table 3** Meta-regression between incidence of mediastinitis and the different study-level and patient-level variables in a univariate analysis

Covariates	Level	$\beta$ -coefficient	SE ( $\beta$ )	Z	$P$ -value
Latitude	Degrees	-0.0020	0.0007	-2.67	0.0075
Age	Years	0.0068	0.0029	2.35	0.018
Female sex	Percent	0.0003	0.0008	0.4367	0.6623
CABG	Percent	0.0006	0.005	1.20	0.2029
Publication year	Year	0.0010	0.0006	1.63	0.1023

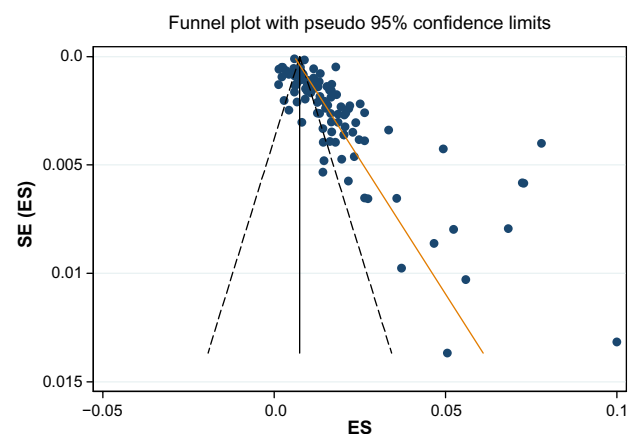
**Abbreviations:** SE, standard error; CABG, coronary artery bypass grafting.

A multivariate meta-regression was performed, which considered study-level and patient-level variables together. This, using random- and mixed-effect models, identified the presence of prospective design, age of the patient, and the latitude of the study as risk factors of DSWI, with 17% of heterogeneity accounted for by these three variables together.

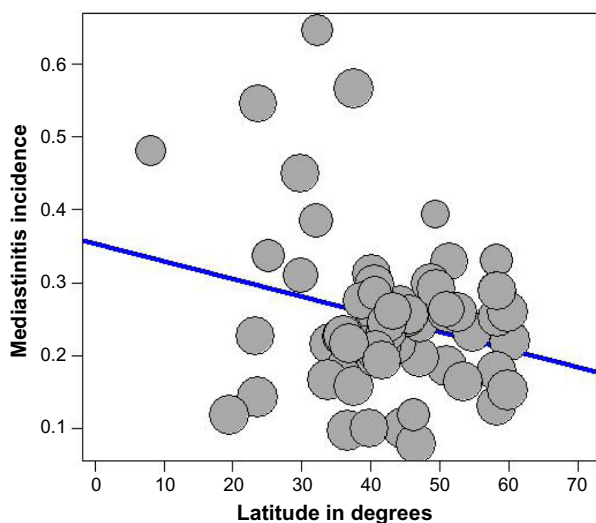
### End points incidence of microorganisms recovered in mediastinitis

#### Gram-positive cocci

Tables 4 and 5 summarize the pooled estimate incidence of Gram-positive cocci in 63 studies using the random-effect model. The incidence was 0.009, 95% CI (0.0081–0.0121), with a substantial heterogeneity. The funnel plot visually showed evidence of bias and small-study effect. This was confirmed by the Begg and Mazumdar rank correlation test ( $P=0.018$ ) and by the Egger's test, which had a  $P$ -value of 0.006 accepting the null hypothesis of small-study effect or selection bias. Because of substantial heterogeneity, we did not correct for selection bias considering the trim and fill simulation method.

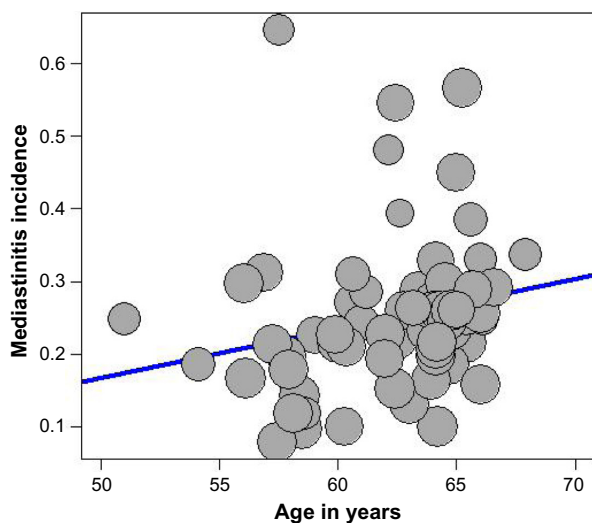


**Figure 2** A funnel plot for the incidence of mediastinitis in 97 studies with Egger line. **Abbreviations:** SE, standard error; ES, effect size.



**Figure 3** Meta-regression of incidence of mediastinitis and latitude of study place. **Note:** Freeman-Tukey double arcsine transformed incidence.

The presence of heterogeneity led us to an investigation of its origin. A stratification analysis on the prospective versus retrospective nature of the cohort and the median latitude of the place of the study showed a significant difference between subgroups. When we extended the analyses with a mixed-effect meta-regression model, one important patient-related variable was identified: age of the patient at sternotomy, with increasing incidence of Gram-positive cocci with increasing age. A multivariate meta-regression was performed, which considered study-level and patient-level variables together. The multivariate mixed-effect model identified age and the prospective nature of the cohort as risk factors of Gram-positive cocci with 16.3% of heterogeneity accounted for by these two variables together.



**Figure 4** Meta-regression of incidence of mediastinitis and mean age of the patient. **Note:** Freeman-Tukey double arcsine transformed incidence.

**Table 4** Estimate of incidence of Gram-positive cocci with stratification on prospective nature of the cohort and latitude of the study place using the random-effect model

Subdivision	n	Incidence (95% CI)	$\tau^2$	$I^2$ (%)	P-value <sup>a</sup>
All studies	63	0.009 (0.0081–0.0121)	0.6067	96.6	
<b>Prospective cohort design</b>					
Yes	33	0.012 (0.0095–0.0167)	0.6219	96.6	0.0078
No/Unclear	30	0.007 (0.0062–0.0097)	0.3392	93.4	
<b>Latitude over median 40°</b>					
Yes	32	0.009 (0.007–0.012)	0.3894	95.7	0.8897
No	31	0.0101 (0.0071–0.0144)	0.964	97.0	

**Note:** <sup>a</sup>Test for subgroup differences using the random-effect model between groups with Q statistics, df = 1, and P-value.

**Abbreviations:** CI, confidence interval;  $\tau^2$ , interstudy variability.

**Methicillin-resistant *S. aureus***

Tables 6 and 7 summarize the pooled estimate incidence of MRSA in 63 studies using the random-effect model. The incidence was 0.0008, 95% CI (0.0005–0.0012), with a substantial heterogeneity. The funnel plot visually showed evidence of bias and small-study effect. This was confirmed by the Begg and Mazumdar rank correlation test with continuity correction ( $P=0.0007$ ) and by the Egger’s test, which had a P-value of 0.0128 accepting the null hypothesis of small-study effect or selection bias. Because of substantial heterogeneity, we did not correct for selection bias considering the trim and fill simulation method.

The presence of heterogeneity led us to an investigation of its origin. A stratification analysis on the prospective versus retrospective nature of the cohort and the median latitude of the place of the study showed a significant difference between subgroups. When we extended the analyses with a mixed-effect meta-regression model, one important study-level variable was identified: the latitude of the place of the study, with decreasing incidence of MRSA with increasing latitude (Figure 5). Also, we identified increasing incidence of MRSA with increasing age of the patients (Figure 6). A multivariate meta-regression was performed, which considered study-level and patient-level variables. The multivariate using mixed-effect meta regression model identified latitude and age of the

**Table 5** Meta-regression model between incidence of Gram-positive cocci and the different study-level and patient-level variables in a univariate analysis using the 63 cohorts

Covariates	Level	$\beta$ -coefficient	SE ( $\beta$ )	Z	P-value
CABG	Percent	0.0110	0.0058	1.89	0.057
Age	Years	0.0889	0.0429	2.07	0.038
Latitude	Degrees	-0.0050	0.0084	0.596	0.5508
Female sex	Yes/No	0.0029	0.0085	0.342	0.7315
Publication year	Year	0.0012	0.0010	1.80	0.2378

**Abbreviations:** SE, standard error; CABG, coronary artery bypass grafting.

**Table 6** Estimate of total incidence of MRSA with stratification on prospective nature of cohort and latitude of the study place using the random-effect model

Subdivision	n	Incidence (95% CI)	$\tau^2$	$I^2$ (%)	P-value <sup>a</sup>
All studies	63	0.0008 (0.0005–0.0012)	1.79	90.5	
<b>Prospective cohort design</b>					
Yes	33	0.0012 (0.0007–0.002)	1.816	91.5	0.0417
No/Unclear	30	0.0005 (0.0004–0.0009)	1.419	83.2	
<b>Latitude over median 40°</b>					
Yes	32	0.0006 (0.0003–0.0010)	1.34	84	0.0853
No	31	0.0011 (0.0006–0.0021)	1.90	84	

**Notes:** <sup>a</sup>Test for subgroup differences using the random-effect model between groups with Q statistics, df = 1, and P-value.

**Abbreviations:** MRSA, methicillin-resistant *Staphylococcus aureus*; CI, confidence interval;  $\tau^2$ , interstudy variability; df, degree of freedom.

patient as independent risk factors of MRSA with 23.13% of heterogeneity accounted for by these two variables together.

### Gram-negative bacilli

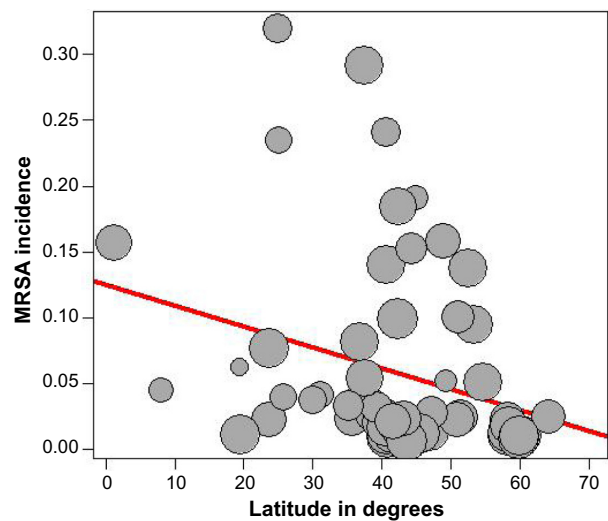
Tables 8 and 9 summarize the pooled estimate incidence of Gram-negative bacilli in 63 studies using the random-effect model. The incidence was 0.0024, 95% CI (0.0018–0.0032), with a substantial heterogeneity. The funnel plot visually showed evidence of bias and small-study effect. The Begg and Mazumdar rank correlation test confirmed this with continuity correction ( $P=0.037$ ) and by the Egger’s test, which had a P-value of 0.00061 accepting the null hypothesis of small-study effect or selection bias. Because of substantial heterogeneity, we did not correct for selection bias considering the trim and fill simulation method.

The presence of heterogeneity led us to an investigation of its origin. A stratification analysis on the prospective versus retrospective nature of the cohort and the median latitude of the place of the study showed a significant difference between subgroups. When we extended the analyses with a mixed-effect meta-regression model, one important study-level related variable was identified: the latitude of the place of the study, with decreasing incidence of Gram-negative bacilli with increasing latitude. A multi-

**Table 7** Meta-regression model between incidence of MRSA and the different study-level and patient-level variables in a univariate analysis using the 63 cohorts

Covariates	Level	$\beta$ -coefficient	SE ( $\beta$ )	Z	P-value
CABG	Percent	0.007	0.005	1.32	0.1848
Age	Years	0.0079	0.0031	2.53	0.0112
Latitude	Degrees	-0.0016	0.0006	-2.53	0.0114
Female sex	Yes/No	-0.0005	0.0007	-0.78	0.4345
Year of publication	Year	0.0140	0.0227	0.61	0.5381

**Abbreviations:** MRSA, methicillin-resistant *Staphylococcus aureus*; SE, standard error; CABG, coronary artery bypass grafting.

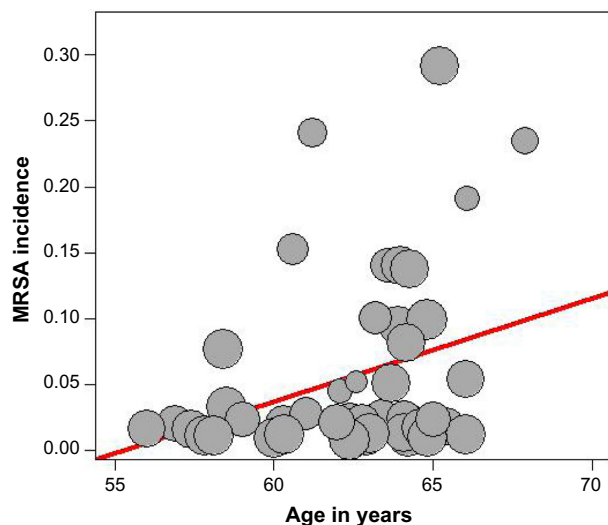


**Figure 5** Meta-regression of incidence of MRSA and latitude of the study place. **Note:** Freeman-Tukey double arcsine transformed incidence. **Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus*.

variate meta-regression was performed, which considered study-level variables also. The multivariate mixed-effect regression model identified latitude and the prospective nature of the cohort as risk factors of Gram-negative bacilli with 14.7% of heterogeneity accounted for by these two variables together.

### Discussion

Our systematic review and meta-analysis of cohorts estimating incidence of DSWI and incidence of different microorganisms after sternotomy showed a high degree of heterogeneity among cohorts for all the outcomes. Also, publication bias or small-size effect was found to influence the outcomes.



**Figure 6** Meta-regression of incidence of MRSA and mean age of the patient. **Note:** Freeman-Tukey double arcsine transformed incidence. **Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus*.

**Table 8** Estimate of total incidence of Gram-negative bacilli with stratification on prospective nature of cohort and latitude of the study place using the random-effect model

Subdivision	n	Incidence (95% CI)	$\tau^2$	$I^2$ (%)	P-value <sup>a</sup>
All studies	63	0.0024 (0.0018–0.0032)	0.9819	91.8	
<b>Prospective cohort design</b>					
Yes	35	0.0058 (0.0053–0.0063)	0.8591	91.9	0.0001
No/Unclear	30	0.0039 (0.0034–0.0043)	1.2000	91.4	
<b>Latitude over median 40°</b>					
Yes	32	0.0018 (0.0012–0.0025)	0.6549	87.4	0.008
No	31	0.0036 (0.0024–0.0054)	1.046	92.4	

**Note:** <sup>a</sup>Test for subgroup differences using the random-effect model between groups with Q statistics, df = 1, and P-value.

**Abbreviations:** CI, confidence interval;  $\tau^2$ , interstudy variability; df, degree of freedom.

Meta-regression analyses indicated that heterogeneity could be explained by patient-related variables and study-level characteristics. For studies reporting on DSWI, the latitude of the study place and age of the patients were important determinants of incidence of this complication. Our results do not support the importance of CABG compared with valve replacement or sex of the patients as associated with incidence of DSWI. Determinants of Gram-positive cocci, including MRSA and Gram-negative bacilli microorganisms, are different. Also, latitude of the study place and age of the patients were determinants for the incidence of MRSA.

## Strengths and limitations

Our review is based on a broad literature search, and it seems unlikely that we have missed relevant studies. Study selection and data extraction, including data assessment, were done by two authors to minimize bias and transcription errors.<sup>118</sup> The major limitation of our study is the quality of cohort studies; it is clear that there is bias introduced by retrospective cohort design. The prospective cohorts showed higher incidence of mediastinitis and specific microorganisms. In the retrospective cohort studies, the accuracy of the parameters recorded and the quality of wound surveillance are therefore variable.

**Table 9** Meta regression model between incidence of Gram-negative bacilli and the different study-level and patient-level variables in a univariate analysis using the 63 cohorts

Covariates	Level	$\beta$ -coefficient	SE ( $\beta$ )	Z	P-value <sup>a</sup>
Latitude	Degrees	-0.0330	0.0108	-3.07	0.002
Age	Years	-0.0466	0.0585	-0.79	0.4261
Female sex	PCT	0.0173	0.0126	1.36	0.1711
CABG	PCT	0.0067	0.0087	0.76	0.4423
Publication year	Year	-0.0092	0.0138	-0.66	0.5055

**Note:** <sup>a</sup>Test for subgroup differences using the random-effect model between groups with Q statistics, df = 1, and P-value.

**Abbreviations:** SE, standard error; CABG, coronary artery bypass grafting; PCT, percentage; df, degree of freedom.

The second problem is a misclassification of the end points DSWI, with some studies pooling DSWIs with infections at other sites, superficial sternal wound infections, or sternal and mechanical complications. Most importantly, all these studies are from different centers. It is likely that selection of patients, choice of procedures, and management of the perioperative period vary greatly among cardiac surgical units. These parameters, although difficult to record, may be important determinants of DSWI. Prospective multicentre studies would ascertain DSWI and identify high-risk patients and procedures and protect cohorts against attrition bias (dropout and loss to follow-up). Another limitation was the impossibility to control the small-study effect due to substantial heterogeneity. Finally, underpowered designed cohorts represented another limitation of our study.

## Problem of heterogeneity due to patient-level and study-level variables on the incidence of mediastinitis and specific microorganisms

### Latitude of the place of the study and temperature-regulated bacterial virulence

Latitude of the study site is a proxy and marker of rainfall, humidity, and environmental mycobacteria that may alter the natural immunity. Latitude and temperature are correlated.<sup>4</sup>

As it was underlined by Shapiro and Cowen<sup>119</sup> for diverse microbial species including viruses, bacteria and fungi temperatures represent a critical environmental factor that is well established. It has been known for some time that temperature is a critical environmental trigger for many bacterial species.<sup>119</sup>

Also, temperature influences developmental transitions in the human fungal pathogen *C. Albicans*'s morphogenetic transition between yeast and filamentous growth and resistance to antifungal drugs.

Eber et al,<sup>120</sup> with data from 132 US hospitals in the period 1999–2006, found that summer season and higher mean monthly outdoor temperature were associated with substantial increases of bloodstream infection. There were increases in monthly count of *S. aureus* including MRSA and other Gram-negative bacteria such as *E. coli* and *Acinetobacter*. This study focused on blood culture to ensure that blood culture reflects infection and not merely colonizing organisms and that the association is with monthly bacterial count and monthly mean temperature, total precipitation, and mean relative humidity. There are several potential explanations of frequency of bacterial bloodstream infections



compared with outdoor temperature levels. First, relatively higher temperatures not  $>37^{\circ}\text{C}$  may facilitate increased growth of bacteria in the environment, which may, in turn, increase colonization of humans.

Mechanisms of bacterial growth and optimal growth temperature vary by organism, which may explain the observed difference in association with outdoor temperature between organisms.

Investigators Mermel et al<sup>121</sup> have observed peaks of community-associated MRSA during summer and autumn and its association with seasonal skin infections. It is well known that each infection agent has an optimal temperature for growth; most grow best at temperature close to  $37^{\circ}\text{C}$ , and too low or too high temperature will not promote growth. Sahoo et al<sup>122</sup> in a time series analysis showed that a combination of weekly average maximum temperature above  $33^{\circ}\text{C}$  coinciding with weekly average relative humidity ranging between 55% and 78% is most favorable for occurrence of skin and soft tissue infections due to *S. aureus* and MRSA, and within these parameters, each unit increase in occurrence of MRSA was associated with increase in weekly average temperature of  $1.7^{\circ}\text{C}$  and weekly average relative humidity of 10%.

Another experimental work done by Madiraju et al<sup>123</sup> challenging MRSA strains in exponential phase cultures by methicillin observed that growth and peptidoglycan synthesis were much more resistant at  $30^{\circ}\text{C}$  than  $40^{\circ}\text{C}$ .

### Latitude of the study place as a marker of surgical and other local practices

The latitude of the place of the study is a marker of operating room practices in open-heart surgery. Surgical procedures as risk factors of mediastinitis were investigated extensively by Eklund et al.<sup>27</sup> The risk of infection in the operating theater is dependent on a lot of factors. One of them the beneficial effect of a preoperative antiseptic shower for reducing the microbial colony count on the patient's skin is still controversial on lowering the infection rate.<sup>124</sup> Shaving the hair from the incision site, especially the night before surgery, is still controversial.<sup>72,125</sup> A Cochrane collaboration review in 2011<sup>126</sup> concluded that when it is necessary to remove hair, the existence evidence suggests that clippers are associated with fewer surgical site infections than razors.

In diabetic patients, during cardiopulmonary bypass, a peak core body temperature  $>37.9^{\circ}\text{C}$  could increase the risk of mediastinitis postoperatively as underlined by Groom et al.<sup>127</sup>

The air contamination control in the operating room<sup>128</sup> is important as contamination of the sternal wound was reduced by 46%, pinpointed by Verkkala et al.<sup>128</sup>

High incidence of glove perforation rates (26%–40%) was found after sternotomy.<sup>129,130</sup>

Also, an incidence of 36% of surgeons' fingertips was contaminated by Gram-positive bacteria.<sup>131</sup> High prevalence of skin recolonization at the end of surgery was highlighted.<sup>129</sup>

There is variability in regimens of antimicrobial prophylaxis throughout the world. Nowadays, the effectiveness of these regimens in reducing SSI is falling short of standard,<sup>132,133</sup> and there is increasing incidence of multiresistant bacteria worldwide.

### Elderly patient and increasing risk of mediastinitis and MRSA

Age of the patients was associated with increasing incidence of total mediastinitis and incidence of specifically Gram-positive bacteria, including MRSA. The elderly patients are a population of people who have a long history of using antibiotics in previous time and have acquired some resistance to these drugs. Suffering from a weakened immune system, the elderly patients are particularly susceptible to all infections, especially MRSA.

In a population study in overall Sweden,<sup>134</sup> the incidence of MRSA per 100,000 inhabitants during the period of 2000–2003 was constant with  $\sim 5$  cases/100,000 inhabitants of 1–59 years and suddenly increased to 10 cases/100,000 inhabitants between 60 and 79 years and to 20 cases/100,000 inhabitants  $>80$  years. This study showed the same trend of increasing incidence by age as in our study on a population of open-heart operated patients.

Elderly patients have high frequency of infectious diseases such as influenza, pneumonia, and urinary tract infection with difficulties in performing early diagnosis because the usual symptoms such as fever and leukocytosis are missing and they are on a high risk of mortality. Little effectiveness of antibiotic treatment in the elderly patients has been shown. On the other hand, there is an alarming upsurge nowadays of antibiotic-resistant bacteria such as MRSA in the community and hospitals and old-people's home institutions.

This strong association between MRSA and mortality among elderly patients is making preventive actions and politics mandatory and of paramount importance. Nowadays, MRSA is a serious threat to public health throughout the world and to the early and long-term outcome of open-heart surgery.

### Conclusion

Evidence from this study suggests the importance of latitude of study place and advanced age as risk factors of

mediastinitis. Latitude is a marker of thermally regulated bacterial virulence and variability of surgical and local practices in open-heart surgery in different places of the world. There is deep concern for the high incidence of mediastinitis and MRSA in the elderly patients undergoing sternotomy, and there is urgent need of preventive action.

## Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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