

Evaluation of the kinetics of Pancreatic Stone Protein as a Predictor of Ventilator-Associated Pneumonia. A post-hoc analysis of BioVAP Study.

Supplementary

Table S1. Posterior summaries of the more relevant parameters and hyperparameters of the joint model 1.

| | Mean | SD | 2.5% | 97.5% | P |
|---|---------|--------|---------|---------|---------|
| Survival process (VAP) | | | | | |
| PSP (normalized to 0-1 range) value | -0.0113 | 0.3851 | -0.7754 | 0.7501 | 0.9649 |
| PSP (normalized to 0-1 range) daily change | -0.1778 | 1.1693 | -2.5444 | 2.0648 | 0.8981 |
| PSP (normalized to 0-1 range) cumulative area | 0.0425 | 0.3929 | -0.7331 | 0.8196 | 0.9009 |
| Infected (vs. Non-infected) | -1.0638 | 0.5657 | -2.2247 | -0.0326 | 0.0431 |
| Longitudinal process for PSP (normalized to 0-1 range) | | | | | |
| Intercept | -2.4376 | 0.6158 | -3.6643 | -1.2383 | 0.0002 |
| N ₁ (days) | 0.3514 | 1.1466 | -1.9007 | 2.5830 | 0.7543 |
| N ₂ (days) | -0.4077 | 0.6505 | -1.7131 | 0.8473 | 0.5211 |
| Infected (vs. Non-infected) | 0.4618 | 0.3856 | -0.2989 | 1.2182 | 0.2341 |
| Apache II | 0.0506 | 0.0160 | 0.0193 | 0.0825 | 0.0011 |
| CRP | 0.0309 | 0.0177 | -0.0033 | 0.0659 | 0.0765 |
| σ | 4.8339 | 0.4396 | 3.9792 | 5.7036 | <0.0001 |

The terms N_i(days) denote the basis for a natural cubic spline with 2 degrees of freedom.

P, tail probability [$2 \times \min\{P(\cdot > 0), P(\cdot < 0)\}$]; PSP, pancreatic stone protein; SD, standard deviation; VAP, ventilator-associated pneumonia.

Table S2. Posterior summaries of the more relevant parameters and hyperparameters of the joint model 2.

| | Mean | SD | 2.5% | 97.5% | P |
|---|---------|--------|---------|---------|---------|
| Survival process (VAP) | | | | | |
| PSP (normalized to 0-1 range) value | 0.0705 | 0.1236 | -0.1729 | 0.3128 | 0.5636 |
| log(CRP) value | -0.0009 | 0.1414 | -0.2802 | 0.2857 | 0.9765 |
| log(PCT) value | -0.0855 | 0.0944 | -0.2784 | 0.0959 | 0.3510 |
| Infected (vs. Non-infected) | -1.0327 | 0.5528 | -2.1590 | -0.0091 | 0.0484 |
| Longitudinal process for PSP (normalized to 0-1 range) | | | | | |
| Intercept | -2.7043 | 0.7220 | -4.1448 | -1.2958 | 0.0001 |
| N ₁ (days) | 0.4515 | 0.5943 | -0.7035 | 1.6011 | 0.4440 |
| N ₂ (days) | 0.2083 | 1.5339 | -2.7473 | 3.2352 | 0.8901 |
| N ₃ (days) | -0.4421 | 1.1345 | -2.7160 | 1.7410 | 0.6944 |
| Infected (vs. Non-infected) | 0.4981 | 0.4123 | -0.3123 | 1.3184 | 0.2277 |
| Apache II | 0.0535 | 0.0171 | 0.0199 | 0.0868 | 0.0030 |
| CRP | 0.0412 | 0.0211 | -0.0002 | 0.0831 | 0.0509 |
| σ | 5.5279 | 0.5040 | 4.5595 | 6.5342 | <0.0001 |
| Longitudinal process for log(CRP) | | | | | |
| Intercept | 1.1246 | 0.2520 | 0.6366 | 1.6243 | <0.0001 |
| N ₁ (days) | -0.2891 | 0.6744 | -1.6260 | 1.0344 | 0.6601 |
| N ₂ (days) | 0.4742 | 0.7043 | -0.8888 | 1.9017 | 0.4933 |
| N ₃ (days) | -0.2065 | 0.7108 | -1.5968 | 1.2052 | 0.7698 |
| Infected (vs. Non-infected) | -0.0740 | 0.1367 | -0.3421 | 0.1931 | 0.5893 |
| Apache II | 0.0010 | 0.0059 | -0.0104 | 0.0126 | 0.8522 |
| CRP | 0.0700 | 0.0071 | 0.0562 | 0.0842 | <0.0001 |
| σ | 0.4544 | 0.0401 | 0.3977 | 0.5524 | <0.0001 |
| Longitudinal process for log(PCT) | | | | | |
| Intercept | -2.2240 | 0.4880 | -3.1840 | -1.2634 | <0.0001 |
| N ₁ (days) | -2.5195 | 1.2760 | -5.0520 | -0.0087 | 0.0495 |
| N ₂ (days) | 0.3525 | 1.0732 | -1.7270 | 2.4686 | 0.7478 |
| N ₃ (days) | 0.5202 | 0.9883 | -1.4281 | 2.4699 | 0.5914 |

| | Mean | SD | 2.5% | 97.5% | P |
|-----------------------------|--------|--------|--------|--------|---------|
| Infected (vs. Non-infected) | 1.1243 | 0.2819 | 0.5747 | 1.6779 | 0.0005 |
| Apache II | 0.0503 | 0.0124 | 0.0259 | 0.0750 | <0.0001 |
| CRP | 0.0592 | 0.0140 | 0.0323 | 0.0868 | 0.0001 |
| σ | 0.8884 | 0.0692 | 0.7919 | 1.0552 | <0.0001 |

The terms $N_i(\text{days})$ denote the basis for a natural cubic spline with 3 degrees of freedom.

CRP, C-reactive protein; P, tail probability [$2 \times \min\{P(\cdot > 0), P(\cdot < 0)\}$]; PCT, procalcitonin; PSP, pancreatic stone protein; SD, standard deviation; VAP, ventilator-associated pneumonia.

Table S3. Posterior summaries of the more relevant parameters and hyperparameters of the joint model 3.

| | Mean | SD | 2.5% | 97.5% | P |
|---|---------|--------|---------|---------|---------|
| Survival process (VAP) | | | | | |
| PSP (normalized to 0-1 range) daily change | 0.7897 | 0.6091 | -0.4067 | 2.0085 | 0.1884 |
| log(CRP) daily change | -0.3548 | 0.5351 | -1.4259 | 0.6670 | 0.5090 |
| log(PCT) daily change | -0.4270 | 0.4359 | -1.3056 | 0.4548 | 0.2979 |
| Infected (vs. Non-infected) | -1.0420 | 0.5599 | -2.1925 | -0.0273 | 0.0417 |
| Longitudinal process for PSP (normalized to 0-1 range) | | | | | |
| Intercept | -2.6909 | 0.7204 | -4.1400 | -1.2891 | 0.0001 |
| N ₁ (days) | 0.4695 | 0.5878 | -0.6733 | 1.6403 | 0.4207 |
| N ₂ (days) | 0.1392 | 1.5120 | -2.7917 | 3.1393 | 0.9316 |
| N ₃ (days) | -0.4724 | 1.1292 | -2.7291 | 1.6850 | 0.6721 |
| Infected (vs. Non-infected) | 0.5094 | 0.4145 | -0.3069 | 1.3229 | 0.2143 |
| Apache II | 0.0534 | 0.0170 | 0.0204 | 0.0874 | 0.0022 |
| CRP | 0.0414 | 0.0211 | 0.0004 | 0.0832 | 0.0480 |
| σ | 5.5677 | 0.5142 | 4.5852 | 6.5960 | <0.0001 |
| Longitudinal process for log(CRP) | | | | | |
| Intercept | 1.1211 | 0.2502 | 0.6377 | 1.6203 | <0.0001 |
| N ₁ (days) | -0.2954 | 0.6789 | -1.6066 | 1.0586 | 0.6502 |
| N ₂ (days) | 0.4777 | 0.7050 | -0.9073 | 1.8777 | 0.4938 |
| N ₃ (days) | -0.2060 | 0.7107 | -1.5896 | 1.1825 | 0.7668 |
| Infected (vs. Non-infected) | -0.0723 | 0.1375 | -0.3397 | 0.1963 | 0.6009 |
| Apache II | 0.0011 | 0.0058 | -0.0102 | 0.0127 | 0.8395 |
| CRP | 0.0700 | 0.0071 | 0.0563 | 0.0843 | <0.0001 |
| σ | 0.4547 | 0.0406 | 0.3980 | 0.5547 | <0.0001 |
| Longitudinal process for log(PCT) | | | | | |
| Intercept | -2.2255 | 0.4851 | -3.1841 | -1.2722 | <0.0001 |
| N ₁ (days) | -2.5026 | 1.2748 | -5.0330 | 0.0579 | 0.0559 |
| N ₂ (days) | 0.3436 | 1.0734 | -1.7958 | 2.4521 | 0.7449 |
| N ₃ (days) | 0.5081 | 0.9853 | -1.4300 | 2.4724 | 0.5963 |

| | Mean | SD | 2.5% | 97.5% | P |
|-----------------------------|--------|--------|--------|--------|---------|
| Infected (vs. Non-infected) | 1.1170 | 0.2841 | 0.5690 | 1.6703 | 0.0005 |
| Apache II | 0.0502 | 0.0124 | 0.0259 | 0.0748 | <0.0001 |
| CRP | 0.0596 | 0.0139 | 0.0325 | 0.0867 | <0.0001 |
| σ | 0.8885 | 0.0686 | 0.7931 | 1.0585 | <0.0001 |

The terms $N_i(\text{days})$ denote the basis for a natural cubic spline with 3 degrees of freedom.

CRP, C-reactive protein; P, tail probability [$2 \times \min\{P(\cdot > 0), P(\cdot < 0)\}$]; PCT, procalcitonin; PSP, pancreatic stone protein; SD, standard deviation; VAP, ventilator-associated pneumonia.

Table S4. Posterior summaries of the more relevant parameters and hyperparameters of the joint model 4.

| | Mean | SD | 2.5% | 97.5% | P |
|---|---------|--------|---------|---------|---------|
| Survival process (VAP) | | | | | |
| PSP (normalized to 0-1 range) value | 0.0512 | 0.1284 | -0.1992 | 0.3053 | 0.6857 |
| PSP (normalized to 0-1 range) daily change | 0.8170 | 0.5902 | -0.3403 | 1.9991 | 0.1522 |
| log(CRP) value | 0.0051 | 0.1423 | -0.2721 | 0.2881 | 0.9741 |
| log(CRP) daily change | -0.3955 | 0.5528 | -1.5180 | 0.6613 | 0.4744 |
| log(PCT) value | -0.0729 | 0.0998 | -0.2840 | 0.1144 | 0.4620 |
| log(PCT) daily change | -0.3792 | 0.4592 | -1.3204 | 0.5350 | 0.3733 |
| Infected (vs. Non-infected) | -1.0386 | 0.5604 | -2.1924 | -0.0085 | 0.0479 |
| Longitudinal process for PSP (normalized to 0-1 range) | | | | | |
| Intercept | -2.7163 | 0.7230 | -4.1716 | -1.3288 | <0.0001 |
| N ₁ (days) | 0.4630 | 0.5936 | -0.6803 | 1.6256 | 0.4340 |
| N ₂ (days) | 0.2092 | 1.4925 | -2.7112 | 3.1962 | 0.9031 |
| N ₃ (days) | -0.4199 | 1.1068 | -2.7088 | 1.7489 | 0.7032 |
| Infected (vs. Non-infected) | 0.5184 | 0.4141 | -0.2838 | 1.3314 | 0.2099 |
| Apache II | 0.0537 | 0.0171 | 0.0200 | 0.0876 | 0.0022 |
| CRP | 0.0412 | 0.0206 | 0.0010 | 0.0818 | 0.0448 |
| σ | 5.5601 | 0.5150 | 4.5787 | 6.5920 | <0.0001 |
| Longitudinal process for log(CRP) | | | | | |
| Intercept | 1.1213 | 0.2498 | 0.6338 | 1.6101 | 0.0001 |
| N ₁ (days) | -0.2857 | 0.6800 | -1.6141 | 1.0488 | 0.6689 |
| N ₂ (days) | 0.4720 | 0.7093 | -0.9294 | 1.8712 | 0.4999 |
| N ₃ (days) | -0.2152 | 0.7192 | -1.6155 | 1.1891 | 0.7544 |
| Infected (vs. Non-infected) | -0.0726 | 0.1362 | -0.3421 | 0.1936 | 0.5958 |
| Apache II | 0.0011 | 0.0058 | -0.0103 | 0.0126 | 0.8568 |
| CRP | 0.0701 | 0.0071 | 0.0560 | 0.0843 | <0.0001 |
| σ | 0.4545 | 0.0404 | 0.3979 | 0.5534 | <0.0001 |
| Longitudinal process for log(PCT) | | | | | |
| Intercept | -2.2212 | 0.4859 | -3.1656 | -1.2535 | <0.0001 |

| | Mean | SD | 2.5% | 97.5% | P |
|-----------------------------|---------|--------|---------|---------|---------|
| N ₁ (days) | -2.5231 | 1.2558 | -4.9786 | -0.0328 | 0.0474 |
| N ₂ (days) | 0.3468 | 1.0678 | -1.7540 | 2.4805 | 0.7427 |
| N ₃ (days) | 0.5168 | 0.9773 | -1.3907 | 2.4386 | 0.5964 |
| Infected (vs. Non-infected) | 1.1149 | 0.2834 | 0.5592 | 1.6675 | 0.0002 |
| Apache II | 0.0502 | 0.0124 | 0.0260 | 0.0748 | 0.0001 |
| CRP | 0.0594 | 0.0139 | 0.0324 | 0.0876 | <0.0001 |
| σ | 0.8874 | 0.0669 | 0.7923 | 1.0546 | <0.0001 |

The terms N_i(days) denote the basis for a natural cubic spline with 3 degrees of freedom.

C-RP, C-reactive protein; P, tail probability [$2 \times \min\{P(\cdot > 0), P(\cdot < 0)\}$]; PCT, procalcitonin; PSP, pancreatic stone protein; SD, standard deviation; VAP, ventilator-associated pneumonia.

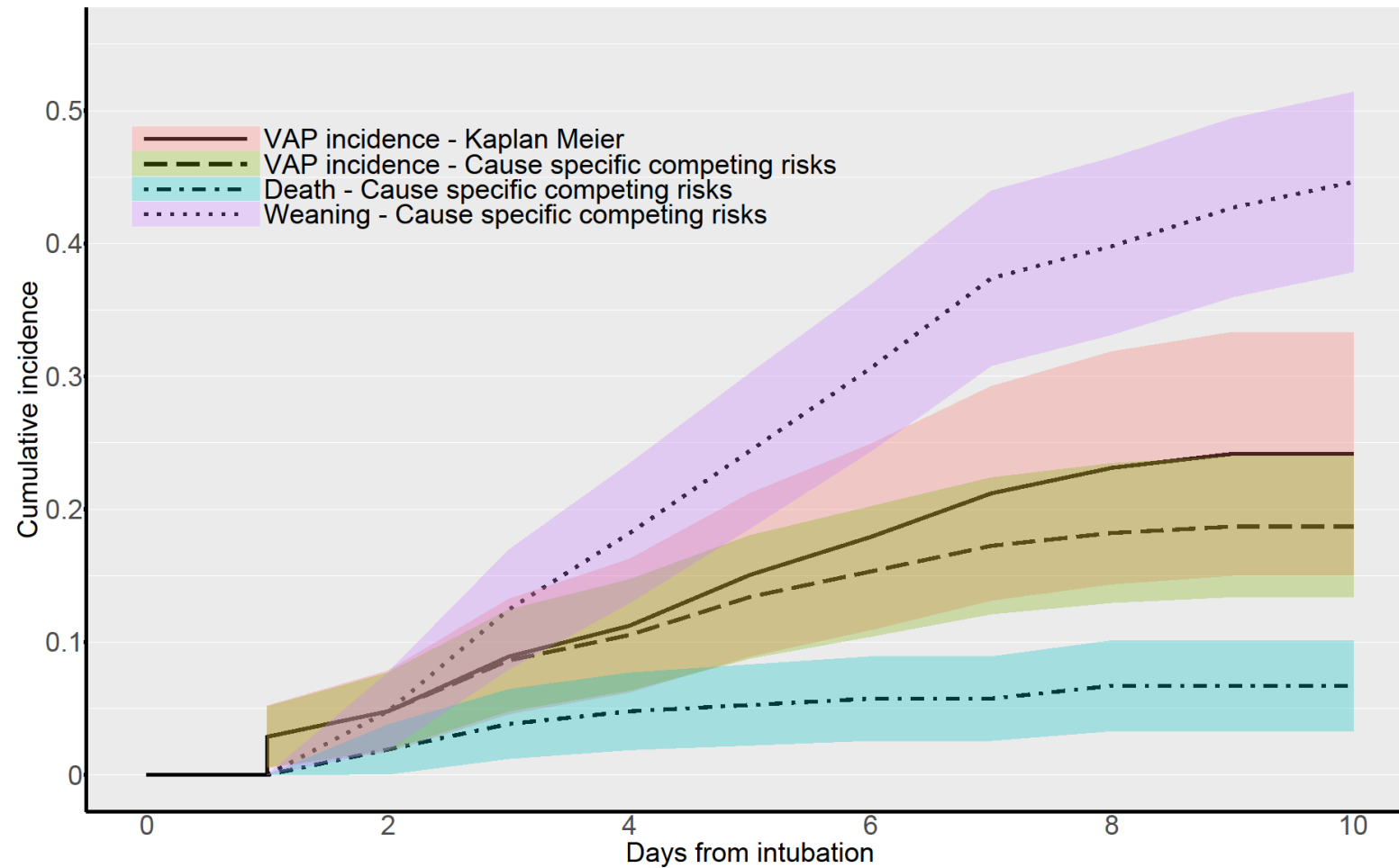
Table S5. Posterior summaries of the more relevant parameters and hyperparameters of the joint model 5, including only patients with non-infection at admission.

| | Mean | SD | 2.5% | 97.5% | P |
|---|---------|--------|---------|---------|---------|
| Survival process (VAP) | | | | | |
| PSP (normalized to 0-1 range) value | 0.3672 | 0.3626 | -0.3121 | 1.1216 | 0.2935 |
| PSP (normalized to 0-1 range) daily change | -0.4091 | 0.9536 | -2.3198 | 1.4156 | 0.6662 |
| PSP (normalized to 0-1 range) cumulative area | -0.4103 | 0.3933 | -1.2248 | 0.3285 | 0.2817 |
| Longitudinal process for PSP (normalized to 0-1 range) | | | | | |
| Intercept | -2.3868 | 0.8871 | -4.1896 | -0.6933 | 0.0060 |
| N ₁ (days) | 0.3692 | 1.7737 | -3.0551 | 3.8709 | 0.8426 |
| N ₂ (days) | -0.8551 | 1.5791 | -4.1242 | 2.1378 | 0.5767 |
| Apache II | 0.0464 | 0.0222 | 0.0029 | 0.0908 | 0.0369 |
| CRP | 0.0142 | 0.0338 | -0.0524 | 0.0805 | 0.6643 |
| σ | 6.8608 | 0.9542 | 5.0099 | 8.7773 | <0.0001 |

The terms N_i(days) denote the basis for a natural cubic spline with 2 degrees of freedom.

P, tail probability [$2 \times \min\{P(\cdot > 0), P(\cdot < 0)\}$]; PSP, pancreatic stone protein; SD, standard deviation; VAP, ventilator-associated pneumonia.

Figure S1. The estimated cumulative incidence of VAP using the Kaplan-Meier approach and the competing risks approach.



The solid line shows the cumulative incidence of VAP calculated using the Kaplan-Meier approach without accounting for competing risk events. The dashed line shows the cumulative incidence of VAP, after adjusting for competing risk. The dotted and dash-dotted lines show the cumulative incidence of weaning and death, respectively.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

| | Item No | Recommendation | Page No |
|---------------------------|---------|---|------------|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | Title page |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed | 4-5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-6 |

| | | | |
|------------------------------|-----|---|-----------------------|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5-6 |
| Study size | 10 | Explain how the study size was arrived at | 5-6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6,7 |
| Statistical methods | 12 | <p>(a) Describe all statistical methods, including those used to control for confounding</p> <p>(b) Describe any methods used to examine subgroups and interactions</p> <p>(c) Explain how missing data were addressed</p> <p>(d) If applicable, explain how loss to follow-up was addressed</p> <p>(e) Describe any sensitivity analyses</p> | 6,7 |
| Results | | | |
| Participants | 13* | <p>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</p> <p>(b) Give reasons for non-participation at each stage</p> <p>(c) Consider use of a flow diagram</p> | 8 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8, 9, 10. Table |

| | | | |
|--------------|-----|--|-------------|
| | | (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount) | 1. Fig 1 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8, 9 |

| | | | |
|--------------------------|----|--|---|
| Main results | 16 | <p>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included</p> <p>(b) Report category boundaries when continuous variables were categorized</p> <p>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</p> | <p>8-10</p> <p>Table 2, Fig 2, 3, and supplementary</p> |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Table 2, Fig 3 |
| Discussion | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 10 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10-14 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 14 |
| Other information | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title page |

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.