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Appraising descriptive and analytic findings of large cohort studies

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Large representative cohorts can provide compelling descriptions of variation in both health care practice and health outcomes, and their value is often underestimated. Such information is vital to health-policy makers for planning services, but also to clinicians and researchers, since substantial variation often represents an opportunity to target improvements in practice and influence future outcomes. In linked research, Devereaux and colleagues report rates of perioperative mortality and serious complications after surgery¹ among people undergoing surgery and requiring at least one night in hospital, adjusted for baseline comorbidities. The scale of the VISION study (>40,000 participants recruited over six years) and the VISION collaboration (which spans six continents) is staggering. However, bias in analyses of observational studies is almost unavoidable and estimates of relationships between complications and mortality should be interpreted carefully before applying their findings to clinical and policy decisions.

Confidence in the results of any study starts with reviewing the authors' prespecified objectives, ideally through registration details and a protocol. The VISION study was established with multiple aims and the registration details (NCT00512109) refer to prognostic analyses of troponin assays,²⁻⁴ making the origins of this report difficult to trace. A statistical analysis plan supplied by the authors in an appendix sets out six objectives, namely, to determine: the incidence of postoperative complications within 30 days after surgery; the time-dependent relationship between these complications and 30-day mortality; the attributable fraction of death at 30 days of each postoperative complication independently associated with mortality; the timing of death during the first 30-days after noncardiac surgery; the proportion of patients who died after noncardiac surgery in-hospital and separately after hospital discharge during a 30-day follow-up period; and the risk of death at 30-days after noncardiac surgery by surgical category.

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3 Four objectives are descriptive while the second and third objectives require analytic
4 quantification of associations between perioperative complications and 30-day mortality.
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8 For descriptive objectives, appraisal needs to focus on recruitment to the cohort and the
9 quality and completeness of the dataset. The VISION study accounts for all patients
10 determined as being eligible, showing that mortality was available for 99.9% (supplemental
11 figure 1). Patients who did not consent made up only 25% of the total, with mainly logistical
12 reasons explaining why others were not enrolled. Here, potential concern about the validity
13 of the descriptive results might arise due to the varied methods of consenting patients across
14 sites. For example, patients at differential risk of perioperative mortality or complications
15 might have been excluded between admission and consent, and not be accounted for.
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18 Findings for analytic objectives need particular scrutiny because several sources of bias can
19 undermine their validity.⁵ Selection into the VISION cohort could also have biased
20 quantification of associations between complications and mortality if patients were excluded
21 for reasons related to the predictor of interest (the occurrence of a complication) and
22 outcome (perioperative mortality).⁵ This might have arisen, albeit for a few patients, if a
23 patient had a complication and died before retrospective consent could be sought.
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26 It is important to consider whether residual confounding can explain the associations
27 observed or bias their magnitude substantially.⁵ In the linked study, hazard ratios (HR) for
28 associations between major bleeding and acute kidney injury with 30-day mortality,
29 estimated with and without adjustment for preoperative haemoglobin and eGFR, suggest
30 some residual confounding in the primary analyses (Supplemental Table 9). The HR for
31 major bleeding (but not AKI) is reduced by adjusting for preoperative haemoglobin and the
32 HR for AKI (but not major bleeding) is reduced by adjusting for preoperative eGFR. These
33 shifts in the HRs are small compared to the overall magnitude of the HRs, so there is no
34 reason to doubt that the associations are real; however, their magnitude may be more
35 uncertain than indicated by their confidence intervals.
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3 Differential misclassification of predictors and outcomes⁵ can happen when outcomes are
4 classified with knowledge of the predictors or vice versa. In the linked study, these risks
5 seem unlikely, since definitions of complications were set out and applied to data that had
6 already been collected, and complications that involved clinical judgement were adjudicated.
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12 Missing data, for predictors, confounders or outcomes, can also introduce bias⁵ but, in the
13 linked study, data were available for 99.0% of the entire cohort. This high percentage may
14 be accounted for by the limited number of predictors included in the model, which in turn
15 introduces the risk of residual confounding. Supplementary analyses adjusting for the
16 additional risk factors preoperative Hb and eGFR show that these preoperative
17 characteristics were missing for 3.4% and 6.8% of patients.
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25 Finally, cherry-picking results from other results generated e.g., from multiple outcome
26 measurements, multiple analyses of the predictor-outcome relationship or different
27 subgroups⁵ is increasingly being recognised as a pervasive source of bias.^{6,7} It is notable
28 that the authors of the linked study had a statistical analysis plan (many analyses of
29 observational cohorts do not) but it is dated some years after recruitment ended (April 2017
30 versus November 2013). There was no selection of results for multiple outcomes or different
31 subgroups but selection of the reported results for relationships between complications and
32 mortality cannot be excluded.
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43 Estimates of the relationships between complications and mortality underpin the calculation
44 of attributable fractions – if the former are uncertain due to potential bias, so are the latter.
45 Attributable fractions should also be interpreted cautiously: basing clinical practice or policy
46 decisions on these statistics requires the user to question closely the plausibility of the
47 assumption that relationships between complications and 30-day mortality are entirely
48 causal. I salute the achievement of the VISION study investigators but advise caution in
49 applying the relationships of complications with 30-day mortality and the attributable
50 fractions.
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9 **Key points:**

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12 1. Descriptions of variation in health care practice and outcome provide extremely
13 valuable information.
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16 2. Estimation of associations between predictors and outcome are at risk of several
17 biases, which must be carefully appraised.
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21 3. The credibility of attributable fractions depends on the validity of the associations on
22 which they are based and the assumption that these associations are entirely causal.
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