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Title page

Haptoglobin administration in cardiovascular surgery patients: its association with the risk of postoperative acute kidney injury

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Institutional Review Board.

The study was not registered prior to patient enrollment.

This report describes an observational clinical study.

This report describes a case control observational clinical study. The

author states that the report includes every item in the STROBE checklist

for case control observational clinical studies.

Unapproved Drugs

Our manuscript was about administration of haptoglobin, which is not yet approved by the FDA. Haptoglobin is commercially available in Japan and is approved by public medical insurance for treatment of hemolysis.

Abstract

Background: Acute kidney injury (AKI) often occurs after cardiac surgery. During cardiac surgery, plasma free hemoglobin would increase due to hemolysis. Since plasma free hemoglobin is thought to be nephrotoxic, haptoglobin, which is a free hemoglobin scavenger, may have the potential to prevent postoperative AKI. However, there have been few studies in which the association of intraoperative administration of haptoglobin with the incidence of AKI after cardiac surgery was assessed.

Methods: This study was a retrospective observational study to assess the independent association of intraoperative administration of haptoglobin with the incidence postoperative AKI in cardiac surgery patients. We screened cardiac surgery patients required cardiopulmonary bypass from 2008 to 2015. We excluded patients required renal replacement therapy preoperatively. We also excluded patients in whom descending aortic replacement was performed. Postoperative AKI was defined according to the Acute Kidney Injury Network

criteria. A propensity score-matched model was used to adjust confounders. For sensitive analysis, we further developed a logistic regression model.

Results: We included 1326 patients in this study. The incidence of AKI in the total cohort was 25.5% (338 patients). Haptoglobin was administered in 260 patients (19.6%). In the crude cohort, the incidence of AKI in patients with haptoglobin administration was 24.6%, which was not significantly different from the incidence of 25.7% in those without haptoglobin administration (p=0.72, odds ratio=0.94 (95% confidential interval 0.69-1.29)). After propensity score matching, we had 249 patients in each group (total of 498 patients). In this propensity score-matched cohort, the incidence of AKI in patients with haptoglobin administration was 22.5%, which was significantly lower than the incidence of 30.9% in those without haptoglobin administration (p=0.033, odds ratio=0.65 (0.43-0.97)). In our logistic regression model for the risk of pAKI, haptoglobin administration was independently associated with decreased risk of AKI (p=0.029, adjusted odds ratio=0.54 (0.31, 0.93)).

Conclusions: In this hypothesis-generating single-center retrospective observational study, intraoperative administration of haptoglobin was independently associated with lower risk of AKI after cardiovascular surgery.

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Introduction

Cardiovascular surgery (CVS) is one of major reasons for acute kidney injury (AKI) (1), the incidence of which has been reported to be approximately 10%-40% (2-4). Since postoperative AKI (pAKI) after CVS is significantly associated with morbidity and mortality (5), the prevention of pAKI is important.

There are many factors that contribute to pAKI after CVS including age, anemia, diabetes, chronic lung disease, chronic heart failure, chronic renal dysfunction, administration of nephrotoxic agents, hypoperfusion, embolization and increased aortic clamp time (6). However, there are few factors that can be treated. Hemolysis frequently occurs in patients who have undergone CVS, especially in those who required CPB (6). Hemolysis leads to an increase in plasma free hemoglobin (fHb), which binds to nitric oxide (NO) (7). Reduced NO due to the increase in fHb would cause microcirculation dysfunction, which may contribute to organ dysfunction such as pAKI (8). Since haptoglobin is a natural fHb scavenger (7), external haptoglobin administration in patients with hemolysis may have the potential to prevent pAKI (9). Furthermore, some studies have

suggested that uptake of the haptoglobin–hemoglobin complex by macrophages may protect against iron-induced tissue injury (10). However, there have been few studies in which the impact of intraoperative administration of haptoglobin on the incidence of pAKI in patients undergoing CVS was assessed (11,12). Accordingly, we conducted a retrospective study to assess the independent association of administration of haptoglobin with incidence of pAKI in CVS patients.

Methods

Design

This study was a single-center retrospective observational study. Kobe University Hospital Ethics Committee approved this investigation. The committee waived the need for informed consent for studies involving the use of a database.

Setting and participants

We screened patients over 20 years old who had undergone CVS with CPB from January 2008 to December 2015 in our hospital. We excluded patients with missing data for perioperative serum creatinine (sCr) levels and relevant confounders, including those died intraoperatively. We also excluded patients who required renal replacement therapy (RRT) preoperatively and patients who had descending aortic aneurysm replacement, because of the presence of renal ischemia during surgery.

Anesthetic management

All of the patients had general anesthesia. None of the patients received premedication. The protocol of anesthesia for CVS in our department is as follows. For induction of anesthesia, patients were anesthetized with 0.5-2 mg/kg of propofol and/or 1-5 mg of midazolam. Then the patients were intubated after administration of 0.6 mg/kg of rocuronium, 1-5 μg/kg of fentanyl and/or 0.1-0.5 μg/kg/minute of remifentanil. For anesthetic maintenance, we gave sevoflurane or propofol, remifentanil, fentanyl and rocuronium. During induction and maintenance, we tried to keep mean blood pressure at more than 65 mmHg. During CPB, blood pressure was also maintained at more than 65 mmHg.

Haptoglobin administration

The attending certificated anesthesiologist decided whether to administer haptoglobin according to the presence of hemolytic urine. Clinically, the anesthesiologist considered the administration of haptoglobin by observing the phenomenon of urinary color becoming red. Usually, 2,000 units of haptoglobin was given. If hemolytic urine persisted, another 2,000 units of

haptoglobin was given. Medical insurance covers up to 4,000 units of haptoglobin in this cohort. Information on the administration of haptoglobin was retrieved and was confirmed by the medical insurance claim.

Data collection

We collected data from electronic medical records for patients' characteristics including age, sex, body weight, preoperative hemoglobin (Hb) level, preoperative estimated glomerular filtration rate (pre-eGFR), left ventricular fractional shortening (FS), Euro Score 2 (13), presence of treated hypertension, diabetes mellitus, atrial fibrillation, previous history of CVS, and preoperative use of intra-aortic balloon pump (IABP). We also collected operative information including information on type of surgery, operation time, duration of CPB, amount of intraoperative red blood cell (RBC) transfusion, and operators.

Outcomes

The primary outcome of this study was the incidence of postoperative

AKI that occurred within 48 hours after the operation. We used preoperative sCr as a baseline value and diagnosed pAKI using the criterion of the Acute Kidney Injury Network: 1) an absolute increase in serum creatinine of 0.3 mg/dL or more or 2) percentage increase in serum creatinine of 50% or more (1.5-fold from baseline) (14). We also categorized patients who required postoperative renal replacement therapy within 48 hours after the operation as pAKI. The secondary outcome was maximum sCr for 48 hours after surgery. Measurement of sCr was routinely done before surgery, immediately after surgery, and in the mornings of postoperative days 1 and 2.

Statistical analysis

The results are shown as median (25-75%, interquartile range(IQR)), n (%) or odds ratio (95% confidential interval (CI)). We divided the patients into two groups according to the administration of haptoglobin. Then, we compared those with and without haptoglobin administration using the Mann-Whitney U test or Chi-square test.

Given the differences between the characteristics of patients with and those without haptoglobin administration, propensity score matching was used to identify a cohort of patients with similar characteristics. The propensity score in the current study was the probability of administration of intraoperative haptoglobin provided from a dataset of covariates. As there was no study to identify the independent predictors of administration of haptoglobin, the propensity score was calculated by a logistic regression model with administration of haptoglobin as a dependent outcome. We used age, sex, weight, preoperative Hb, pre-eGFR, FS, Euro Score 2, presence of chronic hypertension, presence of diabetes mellitus, presence of atrial fibrillation, history of previous CVS, preoperative use of an IABP, year of surgery, type of surgery, emergency operation, operation time, duration of CPB, amount of intraoperative RBC transfusion and operators as covariates. Matching was conducted with a 1:1 matching using nearest-neighbor matching without replacement, with a caliper width equal to 0.02 in propensity score units. We used a structured iterative approach to refine the logistic regression model in order to achieve a balance of

covariates within the matched pairs. We used the standardized difference to measure covariate balance, with an absolute standardized difference above 0.1 representing meaningful imbalance. Then, we compared those with and without haptoglobin administration in matched cohort using the Mann-Whitney U test or Chi-square test.

For sensitive analysis, we further developed a logistic regression model to estimate the independent association of the use of intraoperative haptoglobin with the risk of pAKI. Baseline characteristics related with the incidence of pAKI ($p<0.10$) were chosen and added to the analysis in a stepwise manner.

We used SPSS 20.0 to perform statistical analysis. A p-value <0.05 was defined as a statistically significant difference. Data are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (15).

Results

Study flow

We screened 1740 consecutive patients who had cardiac surgery required CPB (Figure 1). We excluded 135 patients with missing data for perioperative serum creatinine levels and 216 patients who had descending aorta replacement. We then excluded 50 patients who required renal replacement therapy preoperatively. After excluding 13 patients with missing information, we finally included 1326 patients in this study. Postoperative AKI occurred in 338 (25.5%) of the 1326 patients.

Haptoglobin administration and potential confounders

Among the 1326 patients, there were 260 patients (19.6%) who were administered haptoglobin intraoperatively. There were 244 patients who received 2,000 units of haptoglobin and 16 patients who received 4,000 units. Table 1 shows a comparison of demographics for patients with and those without haptoglobin administration. In the crude cohort, patients with administration of

haptoglobin had significantly larger body weight (p<0.001), more likely to have a higher preoperative Hb level (p<0.001), lower pre-eGFR (p=0.03) and premorbid atrial fibrillation (p<0.001), less likely to undergo an emergency operation (p=0.005), had a longer duration of the operation (p<0.001) and CPB (p<0.001), and had a larger amount of red cell blood transfusion (p=0.02) than those without administration of haptoglobin. There was also significant difference in operators between the two groups. There was no significant difference in age, sex, FS, EuroSCORE2, presence of hypertension and diabetes, previous history of CVS, preoperative use of an IABP and surgery type between the two groups.

Primary and secondary outcomes in the crude cohort

In the crude cohort, the incidence of pAKI in patients with haptoglobin administration was 24.6% (64 of 260 patients), which was not significantly different from the incidence of 25.7% (274 of 1066 patients) in those without haptoglobin administration (p=0.72, odds ratio=0.94 (95% CI: 0.69-1.29)) (Table 2). The maximum sCr was not significantly differed between patients with and

without haptoglobin administration (median of maximum sCr; 1.04 (IQR: 0.81-1.31) mg/dL vs 0.98 (0.77-1.34) mg/dL, p=0.58).

Propensity matched analysis

Since we found that significant heterogeneity between the patients with and those without haptoglobin administration, we conducted propensity score matching to adjust for the potentially confounding variables. After propensity score matching, we had selected 249 patients in each group. After propensity score matching, the standardized mean differences were less than 0.1 among all variables. Thus, the covariate balance in the matched cohort appeared to be considerably improved (Table 1). The incidence of pAKI in patients with administration of haptoglobin was 22.5%, which was significantly lower than the incidence of 30.9% in those without haptoglobin administration (p=0.033, odds ratio=0.65 (0.43-0.97)) (Table 2). The maximum sCr was significantly lower in patients with haptoglobin administration in compared with those without haptoglobin administration (median of maximum sCr; 1.01 (IQR: 0.80-1.26) mg/dL vs 1.08 (0.81-1.45) mg/dL,

p=0.035, estimated difference=0.07 (95%CI; 0.01-0.14) mg/dL).

For sensitive analysis, we developed a logistic regression model for the risk of pAKI (table 3). In this analysis, haptoglobin administration was independently associated with decreased risk of pAKI (adjusted odds ratio: 0.54 (95% CI: 0.31, 0.93), p=0.029).

Discussion

Key findings

In the propensity score matching analysis, intraoperative haptoglobin administration was significantly associated with decreased risk of pAKI after cardiovascular surgery. Although this is a hypothesis-generating retrospective study, our study is the first study to show the potential of haptoglobin administration for prevention of pAKI in patients undergoing CVS. Thus, it might be relevant and it requires further discussion.

Comparison with prior studies

There were two studies in which the impact of administration of haptoglobin on renal impairment was assessed (11,12). In a prospective observational study that included 14 patients who underwent cardiac surgery requiring CPB, haptoglobin was administered when fHb exceeded 30 mg/dL. The dose of haptoglobin was not shown in that report. N-acetyl-D-glucosaminidase (NAG) level after haptoglobin administration was 43 mU/mg,

which was significantly lower than the level of 169 mU/mg measured before its administration ($p < 0.05$). They also reported that α1-microglobulin level after haptoglobin administration was significantly lower than that before administration (104 vs 45 micrograms/mg, $p < 0.01$) (11).

A small RCT was carried out to assess the effect of intraoperative administration of haptoglobin. Adult patients scheduled to undergo open-heart surgery with CPB (n=8 for the control group, n=11 for the haptoglobin group) were included in that trial. For patients assigned to the haptoglobin group, 4,000 units of haptoglobin was added to the priming solution of CPB. In the haptoglobin group, NAG at admission to the ICU was significantly lower than that in the control group (0.6 vs 2.5 U/L, $p < 0.01$). Urinary gamma-glutamyltranspeptidase in the haptoglobin group at admission to the ICU was lower than that in the control group (12).

There has been no other study in which the effect of administration of haptoglobin on kidney impairment or function in patients undergoing CVS was

assessed. In this regard, our findings are consistent with results of prior studies, but a novel finding regarding this issue has been added.

Interpretation

We found a significant association of haptoglobin administration with decreased incidence of pAKI. There are several possible explanations for this association. First, the decision to give haptoglobin was made by the physician in charge. Such a selection could bias our results and may not be able to adjust for by using known confounders. However, the physicians used haptoglobin depending on urine color, not the patient's status. Therefore, bias is unlikely.

Second, haptoglobin administration might not have been used for patients with a small amount of intraoperative urine, because urine color could not be recognized for such patients. Haptoglobin administration might also not have been used for patients with diluted urine. Since the amount of intraoperative urine might be associated with the incidence of pAKI, these facts may have skewed our results.

Third, haptoglobin administration might reduce the incidence of pAKI (9). The use of CPB and a cell salvage system and the transfusion of stored red blood cells cause the release of fHb into blood plasma (6). If the concentration of serum Hp, which is a scavenger of fHb, is not sufficiently high, increased serum fHb may cause NO depletion, oxidant stress, and vascular dysfunction (7). Additionally, methemoglobin generated from fHb may damage renal tubules. Furthermore, studies have indicated that uptake of the haptoglobin–hemoglobin complex by macrophages may play a protective role against iron-induced tissue injury by upregulation of CD163 expression, secretion of the anti-inflammatory cytokine IL-10 and upregulation of HO1 expression (10,16). These mechanisms may contribute to renal dysfunction that accompanies hemolysis (8). Accordingly, some studies have shown a relationship between the presence of hemolysis during cardiovascular surgery with CPB and increased risk of pAKI (17,18). A prior study showed that administration of haptoglobin prevented acute kidney injury in cardiac surgery patients (11,12).

Finally, there might be another unknown mechanism or any combination

of the above mechanisms.

Limitations

This study has some limitations. First, this was an observational study in nature, and thus our findings showed an association but not a causality link. Our study, however, might have a potential to generate a hypothesis for establishing methods to prevent pAKI in this cohort.

Second, this was a small single-center study with and weak generalizability. Thus, our finding should be validated outside of study sites.

Third, as we did not have any information to estimate strength of association of haptoglobin with the risk of pAKI, we could not perform sample size calculation prior to conduct current study. The study period was determined by the presence of reliable dataset, then, we included entire patients according to our inclusion criteria. Finally, as our study included 498 patients in propensity matching cohort (249 per cohorts) with 30.9% incidence of pAKI in patients without haptoglobin administration, our study eventually have a 80% power to

detect the 11.3% difference of them with haptoglobin administration. Therefore, our study should be small study with a chance of a type I error. Thus, our findings should be confirmed or refuted by future studies.

Finally, there were no certain criteria for the administration of haptoglobin. Its administration was decided by urinary color becoming red. Thus, mild hematuria might have been overlooked and would have skewed the results. In this regard, a future prospective study should be conducted with an established protocol for haptoglobin administration.

Conclusion

Intraoperative administration of haptoglobin during CVS was significantly associated with lower risk of pAKI in cardiac surgery patients. Since this study was a preliminary hypothesis-generating study, a future study should be conducted to refute or confirm our findings.

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Table 1: Patients' characteristics.

	Before matching				After matching			
	With haptoglobin (n=260)	Without haptoglobin (n=1066)	p-value	standardized mean differences	With haptoglobin (n=249)	Without haptoglobin (n=249)	p-value	standardized mean differences
Age (years old)	70 (62-76)	70 (61-77)	0.93	0.05	70 (62, 76)	72 (62, 77)	0.38	0.003
Male (n)	164 (63.1%)	606 (56.8%)	0.07	0.13	153 (61.4%)	158 (63.5%)	0.64	0.04
Weight (kg)	60.6 (52.3-70.0)	57.3 (48.8-65.6)	<0.001	0.29	60 (52, 69)	60 (51, 67)	0.66	0.09
Hb (g/dL)	13.0 (11.7-14.2)	12.4 (10.9-13.7)	<0.001	0.31	13.0 (11.7, 14.2)	13.0 (11.7, 14.4)	0.57	0.06
eGFR (mL/min/1.73m^2)	86 (70-96)	89 (71-101)	0.033	0.13	86.0 (70.9, 96.5)	88.5 (68.0, 96.5)	0.36	0.06
Fractional shortening (%)	36 (28-43)	36 (29-41)	0.73	0.009	36 (29, 43)	35 (28, 40)	0.21	0.09
Euro score 2 (%)	7 (6-10)	7 (5-9)	0.14	0.12	7 (5, 10)	7 (5, 9)	0.99	0.01
Presence of premorbid hypertension (n)	168 (64.6%)	646 (60.6%)	0.23	0.08	160 (64.3%)	157 (63.1%)	0.78	0.03
Presence of premorbid diabetes mellitus (n)	41 (15.8%)	169 (15.8%)	0.97	0.002	40 (16.1%)	48 (19.3%)	0.35	0.08
Presence of premorbid atrial fibrillation (n)	57 (21.9%)	134 (12.6%)	<0.001	0.25	56 (22.5%)	47 (18.9%)	0.32	0.09
Previous history of cardiovascular surgery (n)	42 (16.2%)	144 (13.5%)	0.27	0.07	36 (14.5%)	43 (17.3%)	0.39	0.08
Preoperative use of IABP (n)	4 (1.5%)	12 (1.1%)	0.58	0.04	4 (1.6%)	2 (0.8%)	0.41	0.08
Aortic Surgery (n)	62 (23.8%)	267 (25.0%)	0.69	0.03	56 (22.5%)	65 (26.1%)	0.35	0.08
Valve Surgery (n)	198 (76.2%)	807 (75.0%)	0.69	0.03	193 (77.5%)	184 (73.8%)	0.35	0.08
Emergency operation (n)	38 (14.6%)	244 (22.8%)	0.0034	0.21	34 (13.7%)	34 (13.7%)	1.00	0.00
Operation time (min)	405 (325-498)	335 (268-411)	<.0001	0.53	401 (324, 483)	388 (322, 479)	0.84	0.03
CPB duration (min)	199 (156-251)	169 (128-211)	<.0001	0.44	197 (155, 246)	189 (152, 243)	0.29	0.09
RBC transfusion (U)	8 (2-14)	6 (0-12)	0.022	0.15	8 (2, 13)	8 (0, 12)	0.69	0.05
Operator 1 (n)	148 (56.9%)	516 (48.4%)	0.014	0.17	140 (56.2%)	141 (56.6%)	0.93	0.008
Operator 2 (n)	45 (17.3%)	188 (17.6%)	0.90	0.009	44 (17.7%)	37 (14.9%)	0.40	0.08
Other operators (n)	67 (25.8%)	362 (34.0%)	0.011	0.17	65 (26.1%)	71 (28.5%)	0.55	0.05
Propensity Score	0.25 (0.16-0.37)	0.15 (0.09-0.23)	<.0001	0.86	0.24 (0.16, 0.34)	0.24 (0.16, 0.34)	0.99	0.002

Hp: haptoglobin, Hb: hemoglobin concentration, RBC: red blood cell, eGFR: estimated glomerular filtration rate (mL/min/1.73m^2)

Table 2: Association of administration of haptoglobin with incidence of postoperative acute kidney injury and maximum serum creatinine.

	Before matching			After matching			
	With haptoglobin (n=260)	Without haptoglobin (n=1066)	p-value	With haptoglobin (n=249)	Without haptoglobin (n=249)	p-value	Estimates of the association
Incidence of pAKI (n)	64 (24.6%)	274 (25.7%)	0.72	56 (22.5%)	77 (30.9%)	0.033	Odds ratio (95%CI) 0.65 (0.43-0.97)
Maximum sCr during postoperative 48 hours (mg/dL)	1.04 (0.81-1.31)	0.98 (0.77-1.34)	0.58	1.01 (0.80-1.26)	1.08 (0.81-1.45)	0.035	estimated difference* (95%CI) 0.07 (0.01-0.14)

Hp: haptoglobin, pAKI: postoperative acute kidney injury, sCr: serum creatinine level

*Estimated difference was calculated using method of Hodges and Lehman (19)

Table 3: Logistic regression model for the risk of postoperative acute kidney injury.

Variable	Odds Ratio (95%CI)	P-value
Haptoglobin administration	0.54 (0.31, 0.93)	0.029
Male	2.39 (1.73, 3.29)	<0.001
Hb (g/dL)	0.79 (0.73, 0.86)	<0.001
Fractional shortening (%)	0.99 (0.97, 1)	0.044
Euro score 2 (%)	1.13 (1.07, 1.19)	<0.001
Presence of premorbid hypertension (n)	1.9 (1.38, 2.63)	<0.001
CPB duration (min)	1.003 (1.001, 1.007)	0.001

CKI: chronic kidney impairment, CI: confidential interval, Hb: hemoglobin concentration, CPB: cardiopulmonary bypass

Figure legend

Figure 1: Study flow.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ***Page 1, 7-9***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***Page 7-9***
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***Page 10,11***
Objectives	3	State specific objectives, including any prespecified hypotheses ***Page 10,11***
Methods		
Study design	4	Present key elements of study design early in the paper ***Page 12***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***Page 12***
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Page 12***
		(*b*) For matched studies, give matching criteria and the number of controls per case

		Nil
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ***Page 14, 15***
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 ***Page 14, 15***
Bias	9	Describe any efforts to address potential sources of bias ***Page 15 – 17***
Study size	10	Explain how the study size was arrived at ***Page 25-26***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ***Page 14 – 17***
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ***Page 15– 17***
		(*b*) Describe any methods used to examine subgroups and interactions ***Nil***
		(*c*) Explain how missing data were addressed ***Page 12***
		(*d*) If applicable, explain how matching of cases and controls was addressed ***Page 15 – 17***
		(*e*) Describe any sensitivity analyses

		Page 17
Results		
Participants	13*	(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
		Page 18
		(b) Give reasons for non-participation at each stage
		Page 18
		(c) Consider use of a flow diagram
		Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		Page 18, 19
		(b) Indicate number of participants with missing data for each variable of interest
		Page 18
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure
		Page 18
Main results	16	(*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
		Page 19, 22
		(*b*) Report category boundaries when continuous variables were categorized
		Not applicable
		(*c*) If relevant, consider translating estimates of

		relative risk into absolute risk for a meaningful time period *Not applicable*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses *Page 21*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Page 22*
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 *Page 26, 27*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence *Page 24-27*
Generalisability	21	Discuss the generalisability (external validity) of the study results *Page 26*
Other information	**Other information**	**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 *Nil*

*Give information separately for cases and controls.

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-stateme