PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomised cross-over cohort study of exposure to emissions from a road tunnel ventilation stack
AUTHORS	Cowie, Christine ; Ezz, Wafaa; Xuan, Wei; Lilley, William; Rose, Nectarios; Rae, Michael; Marks, Guy

VERSION 1 - REVIEW

REVIEWER	Tim Nawrot Associate professor of environmental epidemiology Hasselt University Belgium
REVIEW RETURNED	02-May-2012

THE STUDY	Cowie and colleagues estimated short-term respiratory health effects of exposure to emissions from a road tunnel ventilation stack. The authors used a mixed procedure model to account for the interdependence between subjects on different exposure scenaria including a moment before the tunnel was opened. Initially, 36 subjects participated and 20 on all moments. Comments • no standard deviation is given in Table 2 • the study is original in design but the low number of subjects makes the use of the mixed procedure questionable. Were the residuals normally distributed? The authors should check the procedure assumptions. • The authors made many comparisons and only a few were significant. This is a clear limitation and increase the potential type 1 error. I am not promoting Bonferonni correction but other less conservative methods for multiple adjustments might be considered. The multiple testing should also be mentioned as a limitation.
RESULTS & CONCLUSIONS	The authors studied short term changes. I do not understand why the study runs over 3 years in other words why the different scenaria were tested within such a long period of time.

REVIEWER	Cristina Canova Respiratory Epidemiology and Public Health Imperial College Emmanuel Kaye Building Manresa Road London. SW3 6LR
REVIEW RETURNED	28-May-2012

GENERAL COMMENTS	This is an interesting paper on the short term effect of exposure to emissions from a road tunnel using a randomised cross-over design. The paper is clear and well written. I have just a couple of minor comments. The main comment regards the use of an upwind location as negative control exposure that shows similar and sometimes higher levels of air pollution compared to the downwind location. This issue should be better discussed. I would recommend to include the number of measures for each year in study in Table 2.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Tim Nawrot

1. No standard deviation is given in Table 2

The standard deviation has been added to Table 2.

2. The study is original in design but the low number of subjects makes the use of the mixed procedure questionable. Were the residuals normally distributed? The authors should check the procedure assumptions.

We have checked the residuals which indicated that transformation of the data was not required. An additional sentence has been added to the Methods section on page 14 stating "Examination of distribution of residuals indicated that there were no major departures from normality and that transformation of the data was not required".

3. The authors made many comparisons and only a few were significant. This is a clear limitation and increases the potential type 1 error. I am not promoting Bonferonni correction but other less conservative methods for multiple adjustments might be considered. The multiple testing should also be mentioned as a limitation.

Although multiple significance tests were performed, virtually all the "significant" findings were for the heavily trafficked site, which was the positive control site (where we expected to see adverse effects). Several outcomes were "significant" for this site and the consistency for this site means that the risk of type I error is low.

4. The authors studied short term changes. I do not understand why the study runs over 3 years in other words why the different scenaria were tested within such a long period of time.

Although the study was investigating short term effects associated with exposure to ventilation stack emissions, the study ran over three years because 2006 represented the baseline year and pre-tunnel operation, and 2007 and 2008 represented years where the tunnel was operating. The second follow-up year, 2008, was included as it was expected that traffic volumes in the tunnel would increase between 2007 and 2008. Data collection took place in one year intervals to ensure that seasonal influences were kept as constant as possible. Wording to include the above points has been included on page 7.

Reviewer 2: Cristina Canova

1. The main comment regards the use of an upwind location as negative control exposure that shows

similar and sometimes higher levels of air pollution compared to the downwind location. This issue should be better discussed.

We have expanded on this existing point in the Discussion on page 27.

2. I would recommend to include the number of measures for each year in study in Table 2

This has been included in Table 2. Please note that we have re-run the descriptive analysis after identifying that an older version of the dataset had been used for this initial analysis. This has resulted in slightly differing estimates especially for the symptom scores (not marked as tracked changes in table), however all other analyses and conclusions remain unchanged.

VERSION 2 – REVIEW

REVIEWER	Tim Nawrot Associate Professor Hasselt University Belgium
REVIEW RETURNED	10-Jul-2012

- The Reviewer completed the checklist but made no further comments.

Correction

Cowie CT, Ezz W, Xuan W, *et al*. A randomised cross-over cohort study of exposure to emissions from a road tunnel ventilation stack. *BMJ Open* 2012;**2**:e001201. Spacing in table 3 was inaccurate and missed some header rows. The corrected table is below. Also, in the third paragraph of the section entitled "Health outcomes" the sentence "... higher scores for EYE, CHEST and THROAT symptoms (last row, table 3)" should actually be "higher scores for EYE and CHEST symptoms (table 3)." In addition, the volume number should be listed as "2" in this article. We apologise for these errors.

BMJ Open 2012;**2**:e001201corr1. doi:10.1136/bmjopen-2012-001201corr1

Table 3 Contrasts* in lung function, eNO and symptom scores between the downwind site and the other two sites (upwind and heavily trafficked) adjusted for change from baseline (2006) to subsequent years

Contrast* Location	Year	FEV1 (diff in litres) (95% CI)	FVC (diff in litres) (95% CI)	eNO Ratio (95% CI)	EYE symptoms (diff in score) (95% CI)	THROAT symptoms (diff in score) (95% CI)
Downwind vs (Heavily trafficked and Upwind)†	2007/08 vs 2006‡	0.01 (−0.04–0.06)	0.03 (−0.03–0.09)	1.03 (0.94–1.12)	−0.006 (−0.097–0.086)	0.130 (−0.084–0.344)
	2007 vs 2006	0.03 (−0.03–0.09)	0.05 (−0.03–0.13)	1.01 (0.91–1.11)	−0.055 (−0.159–0.049)	0.041 (−0.220–0.301)
	2008 vs 2006	−0.004 (−0.07–0.06)	0.02 (−0.07–0.10)	1.05 (0.94–1.17)	0.043 (−0.074–0.159)	0.207 (−0.027–0.441)
Downwind vs Upwind	2007/08 vs 2006‡	0.02 (−0.04–0.08)	0.06 (−0.02–0.13)	1.03 (0.93–1.14)	−0.044 (−0.151–0.063)	0.080 (−0.169–0.329)
	2007 vs 2006	0.04 (−0.03–0.11)	0.06 (−0.03–0.15)	1.05 (0.94–1.17)	−0.108 (−0.229–0.012)	−0.006 (−0.308–0.297)
	2008 vs 2006	0.004 (−0.07–0.08)	0.06 (−0.04–0.15)	1.01 (0.89–1.15)	0.015 (−0.120–0.149)	0.179 (−0.092–0.449)
Downwind vs Heavily trafficked	2007/08 vs 2006‡	−0.00 (−0.06–0.06)	0.004 (−0.07–0.08)	1.03 (0.93–1.14)	0.033 (−0.073–0.140)	0.180 (−0.068–0.428)
	2007 vs 2006	0.02 (−0.05–0.09)	0.04 (−0.05–0.12)	0.97 (0.87–1.08)	−0.002 (−0.121–0.117)	0.087 (−0.212–0.385)
	2008 vs 2006	−0.01 (−0.09–0.06)	−0.03 (−0.12–0.07)	1.09 (0.96–1.23)	0.071 (−0.065–0.206)	0.236 (−0.038–0.509)
Heavily trafficked vs (Upwind and Downwind)§	Overall	−0.01 (−0.04–0.01)	−0.03 (−0.06–0.002)	1.09 (1.04–1.14)	0.054 (0.006–0.102)	0.107 (−0.005–0.218)

Contrast* Location	Year	CHEST symptoms (diff in score) (95% CI)	SNEEZE symptoms (diff in score) (95% CI)	DRY NOSE symptoms (diff in score) (95% CI)	SMELL-STRONG Odds ratio (95% CI)	SMELL-ANNOYING Odds ratio (95% CI)
Downwind vs (Heavily trafficked and Upwind)†	2007/08 vs 2006‡	−0.080 (−0.302–0.142)	0.288 (−0.139–0.716)	0.276 (0.040–0.511)	3.45 (1.57–7.60)	1.69 (0.72–3.96)
	2007 vs 2006	−0.031 (−0.277–0.214)	0.375 (−0.093–0.844)	0.320 (0.053–0.587)	5.72 (2.35–13.91)	1.95 (0.77–4.94)
	2008 vs 2006	−0.133 (−0.409–0.143)	0.182 (−0.254–0.618)	0.229 (−0.057–0.516)	2.14 (0.77–5.97)	1.33 (0.44–4.00)
Downwind vs Upwind	2007/08 vs 2006‡	−0.017 (−0.275–0.242)	0.430 (−0.067–0.927)	0.193 (−0.081–0.466)	3.51 (1.40–8.80)	1.23 (0.45–3.40)
	2007 vs 2006	0.033 (−0.252–0.318)	0.422 (−0.123–0.966)	0.187 (−0.124–0.498)	4.11 (1.48–11.43)	1.12 (0.38–3.37)
	2008 vs 2006	−0.042 (−0.362–0.277)	0.424 (−0.080–0.929)	0.178 (−0.154–0.510)	3.31 (0.98–11.18)	1.26 (0.34–4.71)
Downwind vs Heavily trafficked	2007/08 vs 2006‡	−0.143 (−0.400–0.114)	0.147 (−0.349–0.642)	0.358 (0.086–0.631)	3.39 (1.39–8.29)	2.31 (0.90–5.94)
	2007 vs 2006	−0.096 (−0.377–0.185)	0.329 (−0.208–0.866)	0.453 (0.146–0.759)	7.96 (2.89–21.93)	3.38 (1.20–9.54)
	2008 vs 2006	−0.224 (−0.547–0.099)	−0.060 (−0.570–0.450)	0.281 (−0.054–0.617)	1.38 (0.44–4.40)	1.40 (0.41–4.75)
Heavily trafficked vs (Upwind and Downwind)§	Overall	0.209 (0.094–0.325)	0.150 (−0.072–0.372)	0.022 (−0.101–0.144)	2.34 (1.58–3.49)	4.08 (2.67–6.25)

*Contrasts are derived from mixed effects regression model in which location and year, and the interaction between them are fixed effects, and individual subject intercepts are a random effect. Main contrasts of interest are those included in the table and consist of downwind versus other exposures, as the downwind exposure is the primary exposure of interest in this study.
†Downwind vs (heavily trafficked and upwind) is the comparison of downwind versus heavily trafficked and upwind exposures combined.
‡2007/08 vs 2006 represents the comparison of both post-tunnel years combined (2007/08) versus the pre-tunnel year (2006).
§Represents the overall comparison of the heavily trafficked site compared to the upwind and downwind sites combined (data from all years included), as we anticipated the heavily trafficked site to have higher air pollution levels and that health effects would be more prominent.