Respiratory and allergic health effects in a young population in proximity of a major industrial park in Oman

Adil Alwahaibi, Ariana Zeka

ABSTRACT

Background Sohar industrial zone (SIZ), Oman, which started operating in 2006, contains many industries that potentially affect the health of the local population. This study’s aim was to evaluate the health effects in a young population living near SIZ.

Methods Patient visits to state health clinics for acute respiratory diseases (ARD), asthma, conjunctivitis and dermatitis were obtained for the period of 2006 to 2010, for children ages <20 years old, for two large provinces around SIZ. Three exposure zones were defined on the basis of the distance from SIZ determined as: ≤5, >5 to 10, >20 km to represent high, intermediate and control exposure zones, respectively. Age-specific and gender-specific monthly counts of visits were modelled using generalised additive models controlling for time trends. The high and intermediate exposure zones were later combined together due to the similarity of associations. Exposure effect modification by age, gender and socioeconomic status (SES) was also tested.

Results Living within 10 km from SIZ showed a greater association with ARD (risk ratio (RR)=2.5; 95% CI=2.3 to 2.7), asthma (RR=3.7; 95% CI=3.1 to 4.5), conjunctivitis (RR=3.1; 95% CI=2.9 to 3.5) and dermatitis (RR=2.7; 95% CI=2.5 to 3.0) when compared with the control zone. No differences in associations were found for gender and SES groups; greater effects were noticed in the ≤14-year-old group for asthma.

Conclusions This is the first study conducted in Oman to examine the health effects of a young population living near an industrial park. We hope that these findings will contribute in future developments of environmental health policies in Oman.

INTRODUCTION

The accelerated global industrialisation trends during the past century have raised many concerns about the potential environmental health problems that might be caused as a result. In 2012, it was estimated that seven million global deaths per year were attributed to air pollution.1 Enhanced by the lack of strict environmental controls and public health systems in developing countries, industrialisation has shifted in recent decades from developed to developing countries, deteriorating environmental and public health situations in the latter.2 A recent report of the WHO shows that 25% of the mortality in developing countries is environmentally related; this estimate is 17% in developed countries. Children are particularly susceptible to environmental exposures,3 and the WHO’s recent estimates show that 36% of the global child mortality was attributable to environmental causes.4 Oman, one of the currently fast developing economies, has also initiated a heavy industrialisation movement to supplement its national resources, leading to a rapid establishment of several major industrial parks in the country. One of these is the Sohar industrial zone (SIZ), a large petrochemical and heavy metal industrial complex. The establishment of this complex near a densely populated residential area consequently raised great health, environmental and financial concerns from its surrounding residents. SIZ, with its anticipated expansion in the near future, necessitates a parallel community health assessment of the population of the residential area around it. Evidence elsewhere shows that children living near industrial establishments have a higher risk of adverse health outcomes when compared with those living away.5–10 However, global evidence on the risk of adverse health of young populations living in proximity to industries is still limited, as highlighted in a recent review by Pascal et al.11

A recent study, also the first environmental epidemiological study in Oman, showed increased risk of respiratory and allergic disease in an adult population living in proximity to SIZ.12 No similar study has been carried out in Oman to assess the link between the recent industrial developments and child health. The aim of this study was to examine the relationship between adverse health and proximity to SIZ in a young population.

METHODOLOGY

Population data

Daily patient visits to state health clinics in the two provinces around SIZ, Sohar and Liwa, were obtained from the National Al-Shifa electronic system, Oman Ministry of Health (MoH) for the period of 1 January 2006 to 31 December 2010. Information for each patient visit included the consultation date, a unique patient identification number, age, village, health centre and the diagnosis based on the International Classification of Diseases 10th Revision (ICD-10). Ethical approval for this study was obtained from the MoH and Brunel University Ethical Committee.

According to previous evidence on the health effects of air pollution in young populations, we selected to study respiratory and allergic diseases. Respiratory diseases included: acute respiratory diseases (ARD) defined as upper (ICD-10: J0-J06), other acute lower respiratory infections (ICD-10: J20-J22) and pneumonia (ICD-10: J12-J18); and...
asthma (ICD-10: J45 and J46). Allergic diseases included disor-
ders of the conjunctiva (ICD-10: H10-H13), dermatitis (ICD-10: L20-L30) and eczema (ICD-10: L50-L54).

Area-specific population by age and gender for each village
was obtained from the Omani National Census of 2010, and
was used as an offset in the model. The education and occupa-
tional status of the residents was also obtained from the same
source and utilised to define socioeconomic status (SES). Daily
temperature and wind data were provided by the Omani
Department of Meteorology for the entire study period.

Definition of health outcomes variables

For this study, it was important to distinguish between visits for
a ‘new event’ and a ‘follow-up’ for the selected diseases. In
previous epidemiological studies, definitions of a ‘new case’
of ARD in children vary from 1 week disease-free duration to up
to 3 months.13 14 For asthma, many epidemiological studies
define a ‘new asthma attack’ in children as an attack happening
after one attack-free year.15 Other studies have used periods of
1 day,16 2 weeks,17 up to 1 month attack-free for their defini-
tions.18 For allergic diseases, several epidemiological studies
extended their definition of a ‘new event’ from 10 disease-free
days19 to up to 1 year.20 From the above discussion, and also
to ensure sufficient sample size for the analysis, we used a 1 month
time period to define ‘new events’ for ARD, asthmatic and allergic
diseases. Follow-up visits were defined as any patient visit occu-
rating between two ‘new events’.

Site characteristics

SIZ is composed of the Sohar industrial port (SIP) and the
Sohar industrial estate (SIE). SIP contains a petrochemical indus-
trial complex and an iron smelter. The petrochemical complex
started to operate with an oil refinery in 2006, and expanded in
the following 3 years to include the polypropylene, methanol,
formaldehyde, urea and aromatics industries. The main industry
in SIE is an aluminium smelter, which started to operate in
2008. Owing to its early operation date and subjectively visible
plumes, we considered the oil refinery (in SIP) as the centre
point of the industrial park used in the exposure assessment
method.

Exposure assessment

Air pollution monitoring and measurements in the area were
not available for the study period. We employed a proximity
method to classify exposure of the study population according
to their distance from the source of the industrial pollution. The
proximity method has been used frequently in many in-
fluential environmental epidemiology studies with considerable
impact on public health practices and policies.5 21-23 The method
is also used by many environmental regulatory bodies to outline
environmental policies, for example, the US Environmental
Protection Agency environmental exposure risk assessment
framework,24 and the UK Health and Safety Executive in their
planning advice for land use near a major hazard.25 The
method has also been used in the quick assessments of industrial
accidents,26 and in environmental justice studies which often
apply this method in their assessment of environmental
inequality.27

To assist us in determining the exposure categories, we
reviewed previous relevant epidemiological and policy studies.
In some of these studies, the decision of the minimum distance
for the proximity method was arbitrary,11 22-23 using the residents’
complaints of pollutant odours22 or determined by environmen-
tal measurements.30 Definitions of exposure categories in these
studies varied from a 5 to 20 km radius from the industries of
concern.31 22 31 Additionally, we utilised several examples of
international housing policies, which recommend the minimal
safe distance of housings from industrial areas, generally at
>2 km.32

Taking into consideration this previous evidence and to
increase the power of the study, we decided on an incremental
distance of 5 km from the refinery to classify the exposure area
around SIZ. Three exposure zones were defined: high, for those
living ≤5 km from the refinery; intermediate, those living within
>5 to 10 km from the refinery; and control zone as living
greater than 20 km from the refinery. There were no villages located
between 10 and 20 km from the refinery; therefore, this dis-
tance was not represented in the study (figure 1). The use of
only state health data resulted in a small number of cases from
Sohar city, the main metropolitan area of the study provinces. In
its latest statistics, MoH has registered 51 private health clinics
in the study area, out of which 94% were located in Sohar city.
Therefore, the city was excluded from the analysis.

To ensure validity of our proximity exposure definitions, we
constructed monthly wind roses for the study period using wind
speed and direction. The prevailing winds pointed to the west
during summer and September, suggestively carrying the pollu-
tsants farther inland. Wind roses pointed towards the seaside in
winter and November, and had no major direction in the
remaining months. This indicated that during summer and
September, the high and intermediate exposure zones could most
likely reveal similar pollutant patterns.

We also tested a dispersion model of SO2 emitted from the oil
refinery for a very limited period of emission data on pollutant
concentrations (between 1 and 15 January 2008), and other
emission parameters including stack parameters such as number
of stacks, location, height and diameter, emission rate, tempera-
ture and velocity. The model suggested a relative change of two
to four times in the predicted SO2 concentrations for distances
5–10 km, supporting our proximity exposure classification.

Statistical analysis

Monthly event counts were modelled using a generalised addi-
tive model. Modelling diagnostics (Akaike’s Information
Criterion) suggested the use of a negative binomial distribution
to control for the overdispersion in the data. Time, as a month
number, was defined as a continuous variable, and smoothing
splines were applied to capture the non-linear seasonal and
longer term trends in the selected diseases. Positive autocorrela-
tion was detected and controlled with an autocorrelation struc-
ture. We defined three age groups for the analyses: infants as
≤1 year old, children as >1 to ≤14 and young adults as >14 to
<20. Exposure zones (with control zone as the reference) were
coded as factors in the models. The logarithms of gender and
age group-specific population data were used as an offset in the
model.

Mean daily temperature, season and individual years were
tested as potential confounders, and were not found to affect
the exposure–health relationship. This lack of effect could par-
tially be due to the control for time by smoothing function in
the model.

Risk ratio (RR) for the different exposure zones was calcu-
lated as exp(β1) and the 95% CI levels were calculated using the
formula: exp(β1 ± 1.96 x SE). All statistical analyses were carried out
using R software V3.0.0.

Owing to the similarities of the RR between the high and
intermediate exposure zones, further models were carried out
combining the two exposure zones. This was also supported by
the similarity of the likely pollutant spread between the two exposure zones, as suggested by the wind roses and dispersion model.

Sensitivity analysis
To further explore the relationship between exposure and the studied diseases, monthly follow-up frequencies for ARD and asthma were also modelled, using the same model structure and stratified according to age and gender groups.

Assessment of exposure effect modification by age, gender and SES was conducted. SES for each village was determined as the proportions of the total adult population with ‘no education’, ‘high education’ and ‘employment’, which are representatives of the parents’ education and employments. The ‘high education’ index was determined as receiving a bachelor’s degree or above. These indicators were assigned to the study population based on village residency. The distributions of each SES index, across all 59 villages, were divided into two strata: below and above 50%. SES stratified analyses were only carried out for ARD, due to insufficient numbers for other disease definitions.

RESULTS
The total number of visits for the selected diseases was 197,263. The total population-at-risk of census 2010 was 25,215 (table 1). A greater proportion of males in the study population was noted in particular among the ages >1 to <20 years, and it was more pronounced in the high exposure group. A similar pattern of unequal gender distribution was observed in the population-at-risk. A small number of asthma cases was noted in the infants age group.

The results of the model analysis for the association of the number of ‘new visits’ for the selected diseases and exposures are presented in table 2. High and intermediate exposure zones had greater effects for all diseases when compared with the control exposure zone. The consistency in the similarity of the associations for the two exposure zones suggested the feasibility of combining them into one zone of ≤10 km radius from the oil refinery.

Table 3 shows the results of the analysis combining the high and intermediate exposure zones stratified by age category, gender and SES for ARD. Positive associations for all diseases in the combined exposure zone were observed, compared with the control exposure zone. The findings suggested no gender difference in exposure effects and no difference by age for ARD, conjunctivitis and dermatitis. Greater associations were observed for asthma among those aged ≤14 years. No differences in associations for ARD were found for any of the SES definitions.

Table 4 shows the results of the model analysis for the follow-up frequencies of ARD and asthma. Increased follow-up frequencies were observed in the combined exposure zone when compared with the control.

DISCUSSION
This study was carried out to investigate the relationship between adverse health effects in a young population living in

Figure 1  The location of the villages and the industrial zones in the study area. The approximate location of the villages is illustrated. There are no villages located in the area 10–20 km from the refinery. The wind direction is illustrated by the wind rose diagram. SIP, Sohar industrial port; SIE, Sohar industrial estate.
proximity to a new industrial park in Oman. The findings of the study suggested an increase of more than twofold to threefold in the risk of respiratory and allergic diseases among a young population living within 10 km of the industrial park. This geographical dispersion of pollution could be explained by the unfavourable geographic location of SIZ. A recent epidemiological study by Al-Khadouri et al.\(^\text{33}\) reported that the location of SIZ promotes the formation of a stagnant air mass that could travel more than 10 km inland.

Owing to the lack of pollutant emission data for this study, we used the proximity to source for our exposure classification. This approach has been used frequently in many environmental epidemiological\(^5\)\(^\text{21–23}\) environmental policies,\(^24\)\(^25\) and environmental justice studies.\(^27\) This extensive use of the proximity method as an exploratory tool for scoping health effects around industrial areas is mainly because it is simple, fast and more economical, and in our study it was the only way to assess the health effects of this rapidly developing industrial setting.

Our results agree with the existing epidemiological evidence regarding the health effects of the respiratory tract system,\(^5\)\(^\text{2}\) eye\(^6\) and skin\(^7\) of children living near a petrochemical complex. These industries are known to emit a number of environmental pollutants including SO\(_2\), nitric oxides (NO\(_x\)) and volatile organic compounds,\(^\text{34}\) which have been shown to cause skin and mucosal lining irritation, especially of the eyes and respiratory tract.\(^\text{35}\) Several epidemiological studies reveal that children living in the proximity of aluminium and iron smelters are prone to impaired lung function,\(^9\) increased hospitalisation from meteorological study by Al-Khadouri et al.\(^\text{33}\)
respiratory disease, and increased allergic sensitisation and allergic symptoms, most likely related to emitted aluminium and fluoride compounds, SO\textsubscript{2}, NO\textsubscript{x} and heavy metals.

The findings of this study did not show any difference in exposure–disease associations by age groups; an indication of a greater association between asthmatic events and exposure among ages ≤14 years was observed. This is most likely due to the susceptibility of these age groups because of less mature respiratory and immune systems, and also because children spend most of their time outdoors and breathe 50% more air per body mass compared with adults.

A greater number of males aged >1 to <20 years was noted in the exposure zones for both study and at-risk population groups. Gender differences were not as pronounced in the control zone. To understand these patterns, we analysed the Omani census data of 2010 to compare the study population structure with the entire Omani population. The results suggested that the difference in the gender ratio in the study area starts from ages 10 to 14 years, a phenomenon not observed in the entire Omani population. One possible explanation for this greater number of young males in the study area might be due to the increasing labour force migration to this industrial area. This was also supported by the World Bank statistics of 2009, which showed that 87% of the young (aged 15–24 years) labour force in Oman was males.

Table 3 Multivariable analysis* of acute respiratory diseases, asthma, conjunctivitis and dermatitis incidence, in association with the combined exposure zone

<table>
<thead>
<tr>
<th>Exposure groups</th>
<th>Combined† RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARD</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.5 (2.3 to 2.7)</td>
</tr>
<tr>
<td>Males</td>
<td>2.3 (2.1 to 2.7)</td>
</tr>
<tr>
<td>Females</td>
<td>2.6 (2.3 to 2.9)</td>
</tr>
<tr>
<td>≤1 year</td>
<td>2.6 (2.4 to 2.9)</td>
</tr>
<tr>
<td>&gt;1 to ≤14 years</td>
<td>2.4 (2.2 to 2.6)</td>
</tr>
<tr>
<td>&gt;14 to &lt;20 years</td>
<td>2.6 (2.3 to 3.1)</td>
</tr>
<tr>
<td>≤50% ‘no education’ strata§</td>
<td>2.3 (2.1 to 2.6)</td>
</tr>
<tr>
<td>&gt;50% ‘no education’ strata</td>
<td>2.7 (2.4 to 3.0)</td>
</tr>
<tr>
<td>≤50% ‘high education’ strata¶</td>
<td>2.6 (2.4 to 2.9)</td>
</tr>
<tr>
<td>&gt;50% ‘high education’ strata</td>
<td>2.3 (2.1 to 2.5)</td>
</tr>
<tr>
<td>≤50% ‘employment’ strata</td>
<td>2.6 (2.4 to 2.9)</td>
</tr>
<tr>
<td>&gt;50% ‘employment’ strata</td>
<td>2.3 (2.1 to 2.5)</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.7 (3.1 to 4.5)</td>
</tr>
<tr>
<td>Males</td>
<td>3.6 (2.8 to 4.7)</td>
</tr>
<tr>
<td>Females</td>
<td>3.8 (2.9 to 5.1)</td>
</tr>
<tr>
<td>≤1 year</td>
<td>3.6 (2.2 to 6.1)</td>
</tr>
<tr>
<td>&gt;1 to ≤14 years</td>
<td>4.6 (3.8 to 5.7)</td>
</tr>
<tr>
<td>&gt;14 to &lt;20 years</td>
<td>2.6 (1.9 to 3.5)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.1 (2.9 to 3.5)</td>
</tr>
<tr>
<td>Males</td>
<td>2.9 (2.5 to 3.3)</td>
</tr>
<tr>
<td>Females</td>
<td>3.5 (3.1 to 4.1)</td>
</tr>
<tr>
<td>≤1 year</td>
<td>3.3 (2.8 to 3.8)</td>
</tr>
<tr>
<td>&gt;1 to ≤14 years</td>
<td>3.0 (2.7 to 3.4)</td>
</tr>
<tr>
<td>&gt;14 to &lt;20 years</td>
<td>3.8 (3.0 to 4.8)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.7 (2.5 to 3.0)</td>
</tr>
<tr>
<td>Males</td>
<td>2.6 (2.3 to 3.0)</td>
</tr>
<tr>
<td>Females</td>
<td>2.9 (2.6 to 3.3)</td>
</tr>
<tr>
<td>≤1 year</td>
<td>2.8 (2.5 to 3.3)</td>
</tr>
<tr>
<td>&gt;1 to ≤14 years</td>
<td>3.0 (2.7 to 3.3)</td>
</tr>
<tr>
<td>&gt;14 to &lt;20 years</td>
<td>2.5 (2.0 to 3.1)</td>
</tr>
</tbody>
</table>

Study population of ages <20 years, Sohar and Liwa provinces, Oman, 2006–2010. Results are also stratified by age category and gender.

*Adjusted for time trend.
†Follow-ups were defined as any repeated patients’ visits within 1 month of two ‘new event’ visits.
‡Age and gender standardised according to census population figures for 2010.
§Including high and intermediate exposure zones, with control zone as the reference. ARD, acute respiratory diseases CI, confidence interval; RR, risk ratio.

Table 4 Multivariable analysis* of acute respiratory disease and asthma follow-up† in association with the combined exposure zone‡

<table>
<thead>
<tr>
<th>Exposure groups</th>
<th>Combined§ RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARD follow-ups</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.5 (2.8 to 2.7)</td>
</tr>
<tr>
<td>Males</td>
<td>2.5 (2.2 to 2.9)</td>
</tr>
<tr>
<td>Females</td>
<td>2.4 (2.1 to 2.8)</td>
</tr>
<tr>
<td>≤1 year</td>
<td>2.9 (2.6 to 3.2)</td>
</tr>
<tr>
<td>&gt;1 to ≤14 years</td>
<td>2.4 (2.2 to 2.7)</td>
</tr>
<tr>
<td>&gt;14 to &lt;20 years</td>
<td>2.5 (2.1 to 2.8)</td>
</tr>
<tr>
<td>Asthma follow-ups</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.2 (2.5 to 4.0)</td>
</tr>
<tr>
<td>Males</td>
<td>3.2 (2.3 to 4.4)</td>
</tr>
<tr>
<td>Females</td>
<td>3.1 (2.3 to 4.2)</td>
</tr>
<tr>
<td>≤1 year</td>
<td>4.4 (1.9 to 10.1)</td>
</tr>
<tr>
<td>&gt;1 to ≤14 years</td>
<td>3.5 (2.8 to 4.4)</td>
</tr>
<tr>
<td>&gt;14 to &lt;20 years</td>
<td>2.5 (1.6 to 3.9)</td>
</tr>
</tbody>
</table>

Study population of ages <20 years, Sohar and Liwa provinces, Oman, 2006–2010. Results are also stratified by age category and gender.

*Adjusted for time trend.
†Follow-ups were defined as any repeated patients’ visits within 1 month of two ‘new event’ visits.
‡Age and gender standardised according to census population figures for 2010.
§Including high and intermediate exposure zones, with control zone as the reference. ARD, acute respiratory diseases CI, confidence interval; RR, risk ratio.
public and community health around any new industrial parks in Oman would be an appropriate early step to protect population health by the great environmental and health risks posed by this rapid industrial development.37 As a preventive measure, the Omani government has planned to displace the population in proximity of the SIZ industrial park to a different residential area. This measure, involving large economic costs,38 has potential sociocultural and economic implications for the displaced population, which merit further consideration. Future intervention programmes that focus on health protection need to consider these sociocultural factors, in addition to proper planning for environmental monitoring and control.

A few limitations of this study need to be recognised. Owing to the absence of emission data, we used the proximity to source for our exposure classification. The use of this approach might introduce misclassification bias when assigning exposure to population groups as pollutants do not respect boundaries.39 However, we tried to minimise this bias by assessing the potential extent of the pollutant spread utilising wind roses and dispersion model. These distances were also confirmed by similar definitions in previous epidemiological and policy studies.40 Another source of bias was potentially due to the study population loss to private healthcare. However, we think that this source of bias is small in our study, after excluding Sohar city from the analyses. There is great provision and uniform distribution of state health centres (large and medium) in exposure and control zones, which ensure easy access to free healthcare, and only a very limited number of small private clinics (only 3 from a total of 51 private clinics in the larger district).40 Also, excluding Sohar city from the analyses did not affect the study results, confirming the robustness of the data. The use of morbidity healthcare visit data could introduce inaccuracy in defining health outcomes, due to physician inaccuracies in diagnosis, patient comorbidities and the parents’ threshold to seek medical help for their children.41 The latter also depends on sociocultural factors and on accessibility to healthcare. While other factors are more difficult to control in an epidemiological study, the uniformly distributed state health institutions in the study area ensured easy accessibility and most likely uniform reporting and diagnosis of the health conditions studied here.

CONCLUSION
This study is the first environmental health study conducted in Oman to investigate health effects in children living near an industrial complex. This study would hope to mark the start of subsequent environment and health research and monitoring, and to assist in building up evidence for public health practice and environmental health policy in Oman. We also hope that these findings will contribute to a triggering of preventive actions and public health intervention programmes, as well as to global evidence on the effects of industrial development and child health.

Twitter Follow Adil Al-Wahaibi at @adilsaidwahaibi

Acknowledgements The authors wish to thank the considerable contributions from Dr Salim Al-Wahaibi and Dr Hamad Al-Adawi for their help in health data acquisition. The authors also wish to thank Professor Sabah Ahmed Abdul-Wahab Al-Sulaiman (Sultan Qaboos University, Oman) and Joseph S Scire (exponent) for their assistance in the CALPUFF modelling.

Contributors AA carried out the literature review, data collection, design methodology, analysis and paper drafting. AZ supervised and made substantial contributions to the design of the study, analysis, drafting of the paper and revising it critically and also gave the final approval of the version to be published.

Funding AA was funded by the Ministry of Health, Oman through a scholarship for his Doctor of Philosophy (PhD) degree.

Competing interests None declared.

Ethics approval Ministry of Health Oman and Brunel University Ethical Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES


31 Al-Khadouri A, Al-Tahsari S, Charabti Y. Contribution of atmospheric processes to the degradation of air quality: case study (Sohar Industrial Area, Oman). Arab J Geosci 2014;8:1623–33.


