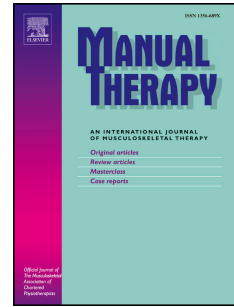


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**Seasonal variation in cervical artery dissection in the Hunter New England
Region, New South Wales, Australia: A retrospective cohort study**

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ABSTRACT

Background: Cervical artery dissection (CAD) is a leading cause of ischemic stroke among middle aged adults, yet the aetiology remains poorly understood. There are reports from colder northern hemisphere sites of a seasonal pattern in the incidence of CAD. Seasonality may suggest some transient putative pro-inflammatory mechanism but it is unknown whether this also exists in temperate climates

Aims: To investigate the seasonal variation in incidence of CAD in the xx Region, Australia, and to compare seasonal incidence and selected clinical features between cases of carotid and vertebral artery dissection.

Methods: This retrospective observational study investigated seasonal variation in CAD from a regional stroke register between 2006 and 2014. Clinical features and site of dissection were dichotomized into autumn-winter and spring-summer groups and compared with Chi² analysis.

Results: 61 CAD events were identified. A strong trend was identified for CAD to occur more frequently in autumn-winter compared to spring-summer (38, 62.30% vs. 23, 37.70%; $p=0.054$). Males were significantly more likely to present with vertebral artery dissection (VAD) than females (27, 73.0% vs 10, 41.7%; $p=0.014$). A history of mild trauma was more common in VAD than internal carotid artery dissection (ICAD) (14, 41.2% vs 3, 13.0%; $p=0.023$). Cases of VAD were more likely to have had an elevated white cell count than ICAD (16, 47.1% vs 5, 20.8%; $p=0.041$).

Conclusions: The findings suggest seasonal variation in the CAD incidence in a temperate region of Australia. Clinicians should be vigilant for CAD or risk of CAD during the colder months.

INTRODUCTION:

Cervical artery dissection (CAD) is a major cause of stroke in young to middle aged adults accounting for 10-20% of ischemic stroke in those less than 50 years (Bejot et al., 2014, Lee et al., 2006, Metso et al., 2009). Its aetiology is multifactorial and remains poorly understood. It is generally considered to involve an underlying susceptibility; such as arteriopathy, a genetic or connective tissue disorder (Arnold et al., 2010, Debette and Leys, 2009), plus exposure to an environmental trigger (Debette, 2014, Schievinck, 2001). Patients commonly present in the early stages with an acute onset of unusual neck pain or headache which may initially be misdiagnosed as a musculoskeletal presentation (Debette et al., 2011, Grond-Ginsbach et al., 2013b, Thomas, 2016).

The majority of CADs occur spontaneously without an obvious precipitating event, despite a frequent but often overlooked association with minor mechanical trauma to the head or neck, including reported links with neck manipulation (Dittrich et al., 2007, Engelter et al., 2013). Patients are typically in their 30-40s, without significant cardiovascular (CV) risk factors, so arterial susceptibility may be hard to predict. Screening for CV risk (Kerry et al., 2008, Rushton et al., 2014) may therefore not offer much protection against dissection. More research is needed to inform clinician's reasoning prior to cervical manual therapy including consideration of other factors, such as infective or inflammatory agents, which might be risk factors for CAD (Grau et al., 1999).

A possible relationship between climate seasons and the incidence of CAD has been investigated in some northern hemisphere countries with very low winter temperatures. Evidence points to CAD being more likely to occur in autumn (Schievinck et al., 1998) or winter (Paciaroni et al., 2006). A recent multi-centre study of 960 CAD patients in Europe found a higher incidence of CAD in autumn/winter compared to spring/summer (56.3% vs 43.7%; $p=0.007$) (Kloss et al., 2012). This suggests that a transient environmental risk factor may be responsible. Possible candidates include recent infection, variations in blood pressure or blood coagulability and viscosity due to colder temperatures. Infections such as chest infections, which tend to be more common in the colder months, can cause transient inflammatory changes in the arterial wall, pre-disposing it to damage either through mechanical factors such as prolonged coughing (Grau et al., 1999, Guillon et al., 2003), neck strain during activities of daily living such as jerky head movements, extreme effort or sporting activities, sustained neck positions or indeed, manipulative therapy procedures (Dittrich et al., 2007, Engelter et al., 2013, Thomas et al., 2015). Fluctuations in blood pressure (Brennan et al., 1982, Jansen et al., 2001), fibrinogen concentration and blood viscosity (Hermida et al., 2003, Kloss et al., 2012, Van Der Bom et al., 1997), also more common in colder temperatures, may increase the potential for thrombosis and vascular events (Hermida 2003).

Seasonality may also differ between dissection of the internal carotid and vertebral arteries (Paciaroni et al., 2006) suggesting a differing mechanism between arteries (Debette et al., 2011). This could be important as the vertebral artery is more vulnerable to minor trauma and has been implicated more commonly in incidents of cervical manipulation (Biller et al., 2014, Debette et al., 2011, Haneline and

Lewkovich, 2005). To date, seasonal variation in CAD has been studied in northern hemisphere countries with cold climates and substantial temperature variations between seasons (Kloss et al., 2012, Paciaroni et al., 2006, Schievinck et al., 1998). No studies have investigated the phenomenon in more temperate climates.

We hypothesised that seasonal variation in CAD also exists in a more temperate climate. If CAD occurs more commonly at particular times of year, this could implicate transient seasonal causes such as infective states and perhaps reduce the emphasis on neck manipulation as a primary cause. If such is the case, the role of pro-inflammatory or hypercoagulable states in dissection would require closer examination and consideration when evaluating patients prior to cervical manual therapy.

This study investigated seasonal variation in incidence of CAD in the temperate region of xx Australia to answer the following questions:

1. Does CAD show seasonal variation in a temperate climate?
2. Is there an association between seasonal variation of CAD and the presence of recent infection, elevated blood pressure indices or environmental influences such as trauma?
3. Does seasonal variation or exposure to risk factors differ between vertebral and internal carotid artery dissection?

MATERIALS AND METHODS:

Study Design

This was a retrospective observational study (case series) using data from an existing database.

Study Population:

All patients aged 18 years and above who were admitted to a public hospital in the xx with a confirmed radiological diagnosis of CAD between January 1st 2006 and December 31st 2014 were included in the study. The xx is a well-defined geographical area of approximately 130,000 square kilometers (similar to the size of England) with a population of 873,717 in 2011 (Australian Bureau of Statistics, 2009). Ethical clearance for the study to obtain access to medical records was gained from the hospital ethics committee; approval no. H-2014-0033.

Data Extraction:

Patients were identified via the xx Cardiac and Stroke Outcomes Unit, which has collected patient data prospectively from July 1st 1995 from all public hospitals in this region. The World Health Organization International Classification of Diseases 10th Revision (ICD-10) was used to classify CAD events. All patients with ICD-10 codes I63.0-6, I63.8-9, I64, I65.0-2, I67.0, I72.0, I72.5, I72.6 were included in the data search to include all potential cases of CAD (Table 1). Each CAD event was assumed to have occurred on the date of symptom onset. For cases where this could not be confirmed, the date of hospital admission was used. Any subsequent admissions within 28 days of the first admission were not included in the data collection. Patients diagnosed with subarachnoid haemorrhage, CAD due to major trauma or CAD of iatrogenic origin were excluded from the study, as these conditions are known to have a differing mechanism. Two researchers (LT; AM) reviewed the

medical records of potentially relevant patients to identify and accept those who met inclusion criteria.

Demographic Data: Data collected on participant characteristics included age, gender, date of presentation, and case fatality within 28 days and 12 months following admission.

Clinical Variables: Clinical features extracted included the site of dissection (i.e. internal carotid or vertebral artery), blood pressure values at time of admission and any history of recent exposure to minor mechanical trauma involving the head or neck. Pathology results including the white cell count and individual leukocyte counts were collected as an indicator of recent infection, as a history of recent infection was not reported consistently in the medical records. Selection of variables was based on possible causative factors for dissection (Debette, 2014, Debette and Leys, 2009, Kloss et al., 2012) and those more likely to be routinely recorded.

Meteorological Data:

Average monthly minimum and maximum temperatures for the study period were accessed from the Australian Bureau of Meteorology, to determine if temperature variation had any effect on monthly incidence rates of CAD. Temperature was chosen as this is reasonably consistent across the region and changes in temperature have been associated with increased rates of infection (Micheli et al., 2010).

Seasons:

Four seasons were defined as described by the Australian Bureau of Meteorology by grouping the calendar months: Spring (1 September to 30 November), Summer (1 December to 28 February), Autumn (1 March to 31 May), Winter (1 June to 31 August).

Statistical Analysis

Age, gender and incidence of CAD grouped by month and season are described using counts and percentages or means (SD) where appropriate. Participants were dichotomized into two seasonal groups (autumn-winter and spring-summer) following the example of previous studies (Kloss et al., 2012). Seasonal incidence and clinical variables were compared between dissection site; Internal Carotid Artery Dissection (ICAD) and Vertebral Artery Dissection (VAD). Proportions of cases, by season, were compared between dissection sites using a Chi-squared test. Comparison of clinical variables between groups was performed with Chi², Fishers Exact, or Mann-Whitney tests as appropriate; the significance level was set at $p \leq 0.05$. Statistical analysis was performed with STATA statistical analysis software (version 11, Statacorp, Texas, USA).

RESULTS:

A total of 743 potential occurrences of CAD were identified from the database based on ICD-10 codes, however only 21 cases were coded specifically for dissection (I67, I72) (Table 1). The remaining cases were coded as more general stroke diagnoses. A review of the medical records of the 743 cases determined a total of 61 occurrences of CAD in 60 participants were eligible for inclusion in the study (one

patient had dissected both VAs 3 months apart). The remaining 682 cases were excluded as they failed to meet radiological confirmation for CAD.

The overall annual incidence of CAD was 0.78 cases per 100,000 individuals in the xx Region. Males were significantly more likely to present with a VAD than ICAD (27, 73.0% vs 10, 41.7%; $p=0.014$). The mean age of the population was 43.3 ± 8.65 years. Although not significant, analysis of all CAD cases revealed a strong trend in seasonality of CAD toward a higher number of CAD events in autumn and winter ($n = 38, 62.3\%$) compared to spring and summer ($n = 23, 37.7\%$; $p=0.054$). This seasonality was more apparent for ICAD cases than VAD (Table 2).

Table 2 presents a comparison of clinical variables between seasonal groups. No significant differences were observed. Nevertheless, exposure to mild trauma was more common in autumn/winter cases than spring/summer cases (37.1% vs 18% $p=0.128$). There was no significant association between clinical features such as blood pressure values and leukocyte counts (as an indicator of recent infection) and seasonality of CAD. Nevertheless, there were slightly more cases with elevated white cell counts in the autumn/winter group.

Seasonal variation and exposure to risk factors were compared between dissection sites. Table 3 presents a comparison of the characteristics of the ICAD and VAD cases. A significantly higher proportion of VAD cases had a history of recent minor mechanical trauma than ICAD cases. These VAD trauma cases occurred more frequently in autumn/winter compared to spring/summer (Figure 1). The trauma reported included post-chiropractic manipulation (4 cases), heavy lifting/carrying (4

cases), sporting injury (2 cases), prior gastric infection with vomiting (2 cases) and wisdom tooth removal (1 case). Cases of VAD were also significantly more likely to have had an elevated white cell count than ICAD and more commonly in autumn/winter.

Meteorological data confirmed the correlation between monthly temperature variation and the incidence of CAD events (Figure 2), suggesting an increased number as temperatures fell during the autumn/winter months.

DISCUSSION:

The study determined that CAD cases in our temperate climate environment were of a similar age and gender to those of northern hemisphere CAD cohorts, although there was a lower incidence of ICAD compared to VAD than recorded in previous studies (Kloss et al., 2012, Paciaroni et al., 2006, Schievinck et al., 1998). There was a strong trend towards seasonal variability with a higher incidence of CAD in autumn/winter compared to spring/summer seasons. A history of exposure to mild trauma was more evident in the autumn-winter group compared to the spring-summer group, suggesting that this risk factor may play a larger role in CAD during the colder months of the year. Other clinical indicators were not strongly associated with seasonal variation in our cohort, although there were significant differences in white cell counts between VAD and ICAD, suggesting possible differing trigger mechanisms between dissection sites. There was a stronger seasonal trend for ICAD than VAD; a history of mild trauma was significantly more likely in VAD, particularly in autumn and winter when compared to ICAD; and elevated white cell counts were significantly more likely in VAD than ICAD.

CAD and seasonal variation

The trend toward a higher incidence of CAD in autumn/winter, although not reaching significance in this study, is consistent with much colder northern hemisphere climates. It appears that individuals may be more vulnerable to CAD in the colder months even in temperate climates, suggesting that extremes of temperature may not be the most important factor, and other factors such as infection may be more important. Therefore, manual therapists and other primary care providers could be more vigilant for CAD as a potential diagnosis in patients presenting with acute neck pain and headache in colder months of the year. Future research to investigate the effects that pro-inflammatory states may have on arterial susceptibility (or vulnerability of the arterial wall) would be useful in this context.

Seasonal variation of clinical variables

Despite the trend toward seasonality of CAD in our cohort, reports of recent infection or potential indicators of recent infection such as elevated leukocyte counts were not different between seasonal groups, albeit there were more CAD cases with raised white cell counts in autumn/winter. This is in contrast to studies which have found a greater incidence of recent infection in autumn and winter in CAD (Grau et al., 1999, Guillon et al., 2003) and may reflect the limited power of our study. Also, we found reporting of details such as previous infection was limited in medical records and blood testing was variable. This limitation has been acknowledged by other authors even in prospective studies (Grond-Ginsbach et al., 2013a). Some suggest that while recent infection is likely to be related to CAD, it may not be related to seasonality (Kloss et al., 2012), so this factor needs further investigation. In relation to other

clinical variables, we found no association between seasonality and elevated blood pressure, in contrast to other studies (Kloss et al., 2012, Pezzini et al., 2006). This may reflect the more temperate climate of the xx Region, where changes in ambient air temperature may not substantially influence brachial pulse pressure (BPP) or mean arterial pressure. The findings of this study therefore offer some insight into the pathophysiology of CAD, suggesting factors such as blood pressure variation may be less important in temperate climates than more extreme climates. However, further research is needed to in larger prospective cohorts to boost power and with more consistent reporting of recent infection and more targeted blood tests in the patient records before definitive advice can be offered to clinicians.

Mild trauma is a known potential risk factor for CAD (Engelter et al., 2013) and its occurrence in our study was proportionately much higher in the autumn/winter group compared to the spring/summer group, although not significantly so. Some authors have attributed winter seasonality of CAD to more vigorous winter sports but this was not the case in our cohort where a variety of activities were involved. This might suggest the underlying arterial susceptibility is the more important causative factor than specific types of trauma, such as manipulation. The role of mild trauma in CAD seasonality therefore remains undetermined and also requires confirmation in larger cohorts.

Nonetheless, while this was a preliminary study and our results were not significant, it may be useful for clinicians to consider recent exposure to minor trauma, or infection involving prolonged coughing or vomiting in their overall evaluation of a patient's suitability for cervical manual therapy, because this might represent a

temporary friability of the cervical arteries making them more vulnerable. However, further research is needed before clear clinical recommendations can be made.

Differences between VAD and ICAD

There were more ICAD cases in autumn/winter than in spring/summer, whereas VAD was somewhat more evenly distributed between seasons (21 cases vs. 16 cases) which supports previous reports of greater seasonal influence with ICAD (Paciaroni et al., 2006). The higher proportion of VAD cases with exposure to mild trauma suggests that this risk factor plays a greater role in VAD than ICAD, though its link with seasonality is inconclusive. Some suggest a link with winter sports perhaps due to the greater potential for falls or contact injuries (Kloss et al., 2012). This finding reflects those of DeBette et al. (2011) who speculate this to be the result of the anatomical differences between the arteries, with the vertebral artery running a more tortuous course through the upper cervical vertebrae and therefore more likely affected by strain on the neck.

Though recent infection or elevated white cell counts did not show seasonality in our study, white cell counts were significantly higher in VAD than ICAD, suggesting pathophysiological mechanisms may differ between the two.

Strengths and Limitations:

This study provides unique information about seasonal patterns or risk factors of CAD in a more temperate climate, and identifies that while seasonality appears similar, risk factors may differ from colder climates.

There are some limitations to this present study. The sample size was modest, which limited the statistical power of between season and subgroup analyses. Therefore, findings should be interpreted with caution and considered as preliminary until higher numbers of cases can be collected. Coding limitations made it extremely difficult to identify dissection cases, as many were coded under more general stroke codes. This problem has been highlighted by other authors (Cai et al., 2014). It is possible that not all CAD cases were identified in the registry in the defined period, which may explain differences in overall incidence, lower ratio of ICAD to VAD, and higher number of male participants with VAD to that previously reported. Likewise, inconsistencies in recording clinical variables such as history of infection and blood testing in the medical records limited our ability to accurately investigate the seasonal associations of this clinical variable. These limitations highlight the need for better identification of stroke sub-types through coding systems and improved data collection practices, to allow better investigation of pathophysiological mechanisms for less common pathologies such as CAD. These limitations could be averted in a prospective study, with active surveillance for CAD cases in hospital.

CONCLUSION:

There is a trend towards CAD having a seasonal variation in a temperate climate with higher incidence in autumn/winter; this is consistent with the pattern seen in the northern hemisphere. Some differences in seasonal risk factors were found, for example, exposure to recent trauma in VAD suggesting clinicians should be more vigilant for this condition in the colder months and consider using greater caution with more vigorous manual techniques. This study provides the framework for future

prospective studies with larger patient numbers to better understand the pathophysiological mechanisms of CAD.

CONFLICTS OF INTEREST:

None to declare.

TABLES AND FIGURES LEGEND:

- Table 1** ICD-10 codes included in data search of xx Cardiac and Stroke Outcomes Unit register
- Table 2** Comparison of participant characteristics between autumn-winter and spring-summer groups
- Table 3** Comparison of participant characteristics between internal carotid and vertebral arterial dissection cases
- Figure 1** Frequency of exposure to mild trauma in autumn-winter and spring-summer CAD events between internal carotid and vertebral arterial dissection
- Figure 2** Meteorological data mean temperatures for xx 2006-2013 with overlay of CAD events by month suggesting increased events as temperatures fell (visual analysis only).

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Table 1 ICD-10 codes included in data search of xx Cardiac and Stroke Outcomes

Unit register.

I65.0	Occlusion and stenosis of vertebral artery
I65.1	Occlusion and stenosis of basilar artery
I65.2	Occlusion and stenosis of carotid artery
I67.0	Dissection of cerebral arteries, nonruptured
I72.0	Aneurysm and dissection of carotid artery
I72.5	Aneurysm and dissection of other precerebral arteries
I72.6	Aneurysm and dissection of vertebral artery

Table 2. Comparison of participant characteristics between autumn–winter and spring–summer groups.

Participant characteristic	Autumn-Winter n= 38	Spring-Summer n = 23	p-value
<i>Demographics</i>			
Gender (Male) (%)	21 (55.3%)	16 (69.6%)	0.268
Age (mean, SD) (years)	43.8 (8.07)	42.4, (9.66)	0.522
<i>Site of Dissection</i>			
ICAD	17	7	0.268
VAD	21	16	
<i>Clinical Variables</i>			
Mild trauma, y	13 (37.1%)	4 (18.2%)	0.128
Raised Leukocyte count(any)	21 (55.3%)	10 (43.5%)	0.503
Raised WCC	13 (35.1%)	8 (38.1%)	0.822
Raised Neutrophil	17 (46.0%)	8 (38.1%)	0.562
Raised Lymphocyte	1 (2.7%)	0	1.000
Raised Monocyte	6 (16.2%)	3 (14.3%)	1.000
SBP (mean, SD)	141.8, (22.1)	145.6, (25.5)	0.787
DBP (mean, SD)	84.9, (14.8)	84.1, (13.0)	0.842
MAP (mean, SD)	83.24 (43.0)	79.4 (44.8)	0.917
PP (mean, SD)	48.6, (33.7)	51.8, (45.1)	0.805

SBP – Systolic Blood Pressure, *DBP* – Diastolic Blood Pressure, *MAP* – Mean Arterial Pressure, *BPP* – Brachial Pulse Pressure.

Table 3. Comparison of participant characteristics between internal carotid and vertebral arterial dissection cases.

Participant characteristic	Total	ICAD n=24	VAD n=37	p-value
Age, y (mean, SD)		43.5 ± 9.9	43.2 ± 7.9	0.924
Male (%)	37	10 (27.0%)	27 (73.0%)	0.014*^α
Female (%)	24	14 (58.4%)	10 (41.7%)	
<i>Seasonal Cases</i>				
Autumn	16	6	10	0.572
Winter	22	11	11	
Spring	11	4	7	
Summer	12	3	9	
A/W Combined	38	21	17	0.268
S/S Combined	23	16	7	
Exposure to mild trauma, y	17	3 (13.0%)	14 (41.2%)	0.023*^α
Elevated white cell count	21	5 (20.8%)	16 (47.1%)	0.041*

*Denotes significant finding. ^αp-value result from Chi² 2x2 Table analysis

Figure 1

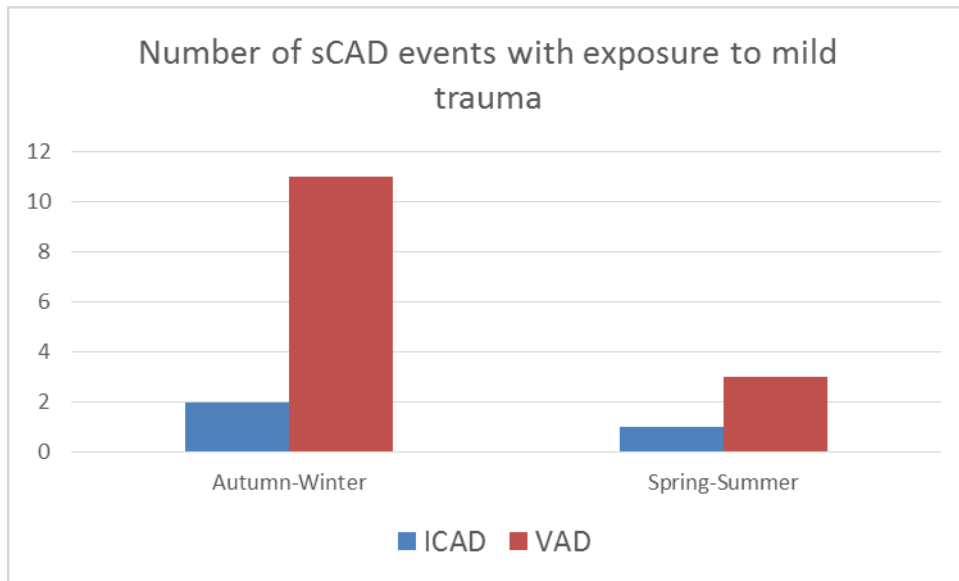
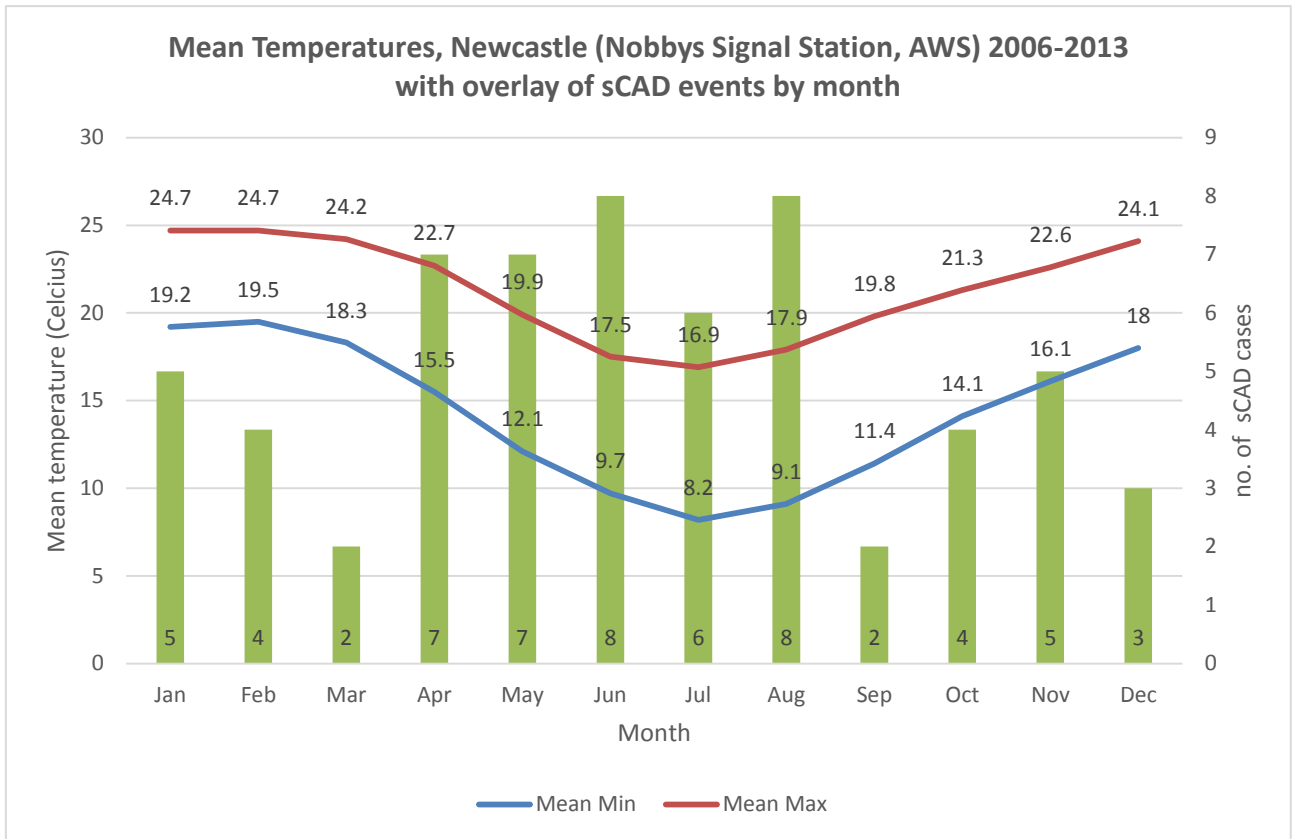


Figure 2.



HIGHLIGHTS

- CAD may occur more commonly in the colder months -autumn/winter
- Exposure to recent trauma was more common in cases of VAD in autumn/winter
- Be caution with manual techniques in autumn/winter following recent infection
- Be vigilant for potential of CAD in autumn/winter particularly following recent infection