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Prevalence of Self-reported Polycystic Ovary Syndrome and Profiles of Health Among Women of Different Generations: A Cross Sectional Study

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ABSTRACT

Objective: Although polycystic ovary syndrome (PCOS) is considered a lifelong disorder, very little is understood about the diagnosis and impact of this condition in women outside of the peak reproductive years. We examined the frequency of diagnosed PCOS and concurrent health conditions in women across the lifespan.

Methods: Data were analysed from 1509 women aged 15–95 years participating in a cross-sectional, face-to-face population survey in South Australia, 2015. We assessed the prevalence of PCOS in 10-year age groups and the frequency of comorbidities in women with and without PCOS subgrouped by age (< 45, \geq 45 years). The main outcome measures were Diagnosed PCOS and other chronic conditions; lifestyle factors. Logistic regression analyses determined the risk of comorbidities in women with PCOS adjusting for age and BMI.

Results: Overall prevalence of PCOS was 5.6% (95% confidence interval (CI) 4.6–6.9%), peaking in the 35–44 year age group (9.1%), and lowest in those aged 15–24 (4.1%) or \geq 65 (3.7%) years. Women with PCOS and aged < 45 years were more likely to report diabetes (16.7% vs. 3.8%), cardiovascular disease (15.5% vs. 7.2%) and arthritis (15.5% vs. 7.2%) than their peers; these differences were diminished in the \geq 45 year age group. The odds of diabetes and cardiovascular disease were more than doubled among women with PCOS (adjOR 2.23, 95% CI 1.49–4.31; adjOR 3.18, 95% CI 1.31–7.68).

Conclusion: PCOS is underdiagnosed in young and post-menopausal women. Diabetes and cardiovascular disease are key comorbidities requiring greater attention in younger women with PCOS.

Keywords: Polycystic Ovary Syndrome; Comorbidities; Chronic Health Conditions; Age Factors; Diagnosis.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder that manifests in an array of symptoms that varies from one woman to another. Common symptoms of PCOS include menstrual irregularities, excess hair growth (hirsutism), acne, and weight gain (Escobar-Morreale, 2018); these are driven by an excess of androgens (hyperandrogenism) and insulin resistance, which are central features of the condition. Historically PCOS was considered a reproductive disorder acquired by adult women, but it is now understood to be a lifelong metabolic condition (El Hayek et al., 2016). PCOS is estimated to affect 6 to 18% of women, depending on the diagnostic criteria used (Teede et al., 2010; March et al., 2010). However, in older generations of women, diagnosis typically occurred only if women sought fertility treatment (Lujan et al., 2008). Better recognition of the syndrome across clinical specialties, and less reluctance by women to disclose symptoms, has improved diagnosis in women currently of reproductive age.

Relatively little is known about the progression of health status of older women with PCOS. Available evidence suggests that they may have relatively early onset of diabetes and other cardiometabolic

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disorders, only partly accounted for by the tendency for women with PCOS to be obese (Daan et al., 2014). There is some evidence that women with PCOS perceive their health to be poor (Bazarganipour et al., 2013) and their lifestyle behaviours are less healthy than those of their peers (Lin et al., 2018) which may also contribute to agerelated deterioration in health (Echiburu et al., 2016). Among young women with PCOS, poor mental health and emotional distress has consistently been documented (Barry et al., 2011; Blay et al., 2016; Dokras et al., 2011, 2012; Veltman-Verhulst et al., 2012) but it is unclear whether psychological problems prevail with age.

Most of the published research on PCOS has been based on highly selected groups of women drawn from clinics. Such groups are known to comprise of women with the most severe disease states (Azziz et al., 2016). Consequently, information is lacking about women with PCOS in unselected populations across the lifespan (Azziz et al., 2016). This impedes progress in understanding the burden of this condition in the community and the presentation of phenotypes of PCOS, particularly in peri- and post-menopausal women.

The aims of this paper are two-fold. First, to describe the prevalence of self-reported, doctor-diagnosed PCOS across 10-year age groups in a representative, community-based sample of women aged 15 to 95 years. Second, we aimed to explore the extent to which women with PCOS experienced increased physical, metabolic and psychological comorbidities compared to women without PCOS, and whether any excess risk persists as women age.

METHODS

This study utilised data from the 2015 South Australian Health Omnibus Survey, an annual, population-based survey of approximately 3000 males and females, designed to be representative of the South Australian population aged over 15 years (Wilson et al., 1992). A different sample of respondents are selected each year. Details of the methodology and characteristics of the sample have been reported elsewhere (Wilson et al., 1992). Briefly, participants were identified using a multistage process of clustered, selfweighted sampling of households in metropolitan and country areas with populations of more than 1000. Data were weighted by 5-year age groups, sex, and area (metropolitan Adelaide and rural/ remote South Australia) to the most recent Estimated Residential Population for South Australia (Australian Bureau of Statistics, 2013) and by the probability of selection within the household size to provide population estimates. Interviews were conducted in person by trained interviewers. These analyses use only data from female respondents, and 2015 was the first year that questions about PCOS were asked.

Measures

Diagnosis of polycystic ovarian syndrome

The presence of PCOS was determined by asking women "Have you ever been diagnosed with Polycystic Ovary Syndrome?" This implied that the women had visited a doctor and received a diagnosis.

Demographic and lifestyle characteristics

Demographic variables were used for weighting purposes and to describe the sample. Participants reported their country of birth, age, marital status, household size, highest education level achieved, annual household income, current employment status and whether they were of Aboriginal or Torres Strait Islander origin.

In the analyses age was classified in two ways: 10-year age groups (15–24, 25–34, 35–44, 45–54, 55–64, \geq 65 years), or two age categories, < 45 years and \geq 45 years. The latter subgroups distinguish women according to reproductive and peri-/post-menopausal years.

Women self-reported their height (cm) and weight (kg). Body mass index (BMI) was calculated (weight/height²) and then categorised using World Health Organization criteria for respondents \geq 18 years (BMI \geq 25 kg/ m² for overweight and obesity, BMI \geq 30 kg/m² for obesity (World Health Organization, 2000)) and corresponding categories for respondents aged < 18 years (Cole et al., 2000).

Women reported their current physical activity status (whether they exercised >3 days/week) and current smoking status (affirmed if they smoked daily or occasionally). Women were also asked if they had ever been pregnant.

Physical, metabolic and psychological comorbidities

Metabolic and other chronic conditions were assessed by asking respondents if they had ever been told by a doctor that they had diabetes, cardiovascular disease (CVD) (specifically heart attack, angina, stroke and/or atrial fibrillation), arthritis (osteoarthritis, rheumatoid arthritis or any other type), asthma (affirmed if currently have asthma), or had been prescribed medication for high blood pressure or cholesterol.

Self-rated health status (dichotomised to poor/fair or good/very good/excellent) was derived from the first question of the Short Form 12 (SF12) (Ware et al., 1996): a generic, multipurpose questionnaire concerning views on health status over the past 4 weeks). Women were classified as having clinical symptoms of depression if they had scored below 42 on the Mental Component Summary of the SF12 (Silveira et al., 2005). Participants also reported any current use of antidepressant medications.

Statistical analysis

The prevalence of diagnosed PCOS was calculated for the overall sample. Sociodemographic and lifestyle characteristics of women diagnosed with PCOS were then compared with those without PCOS using Pearson's chi-square tests for association for categorical data. The prevalence of PCOS in each 10-year age strata with 95% confidence intervals (CIs) was plotted.

Women were subgrouped by age (< 45 years or \geq 45 years) to indicate the end of reproductive years and commencement of perimenopause, and differences in the frequency of physical, metabolic and psychological comorbidities and fair/poor self-assessed health by PCOS status were examined using Pearson's chi-square tests for association (and Fisher's exact correction where cell sizes were less than 5). A p-value of < 0.05 was considered significant.

Overall differences in the risk of physical, metabolic and psychological comorbidities and poor/fair self-assessed health between women with and without PCOS were examined using logistic regression. Odds ratios (OR) and 95% CI were generated in unadjusted models, then adjusted for age (six categories, 10-year age bands), and age and BMI status (continuous), as both of these factors contribute independently to the risk of chronic health conditions (Xu et al., 2018). All analyses were conducted using SPSS Version 22.0 (SPSS, 1989–2016).

RESULTS

In 2015, 1527 women aged \geq 15 years completed the survey, with an overall response rate of 57.3%. Seventeen women did not answer the question on PCOS (1.1%) so were excluded from further analyses. Table 1 describes the sociodemographic and lifestyle characteristics of the sample (n = 1509). The mean age was 47.4 years (SD 19.3), most respondents were born in Australia (73.7%) and were married or living with a partner (63.2%). Approximately one quarter had a tertiary (university) qualification (24.9%). Eight-five women (5.6%, 95% CI 4.6–6.9%) reported a diagnosis of PCOS. There were no

Table 1. Demographic and lifestyle characteristics of the	
study sample, subgrouped by self-reported PCOS status.	

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21.0) 30 28.4) 49	01 (21.1)	17 (19.8)	
28.4) 49	05 (00 1)		
	95 (28.4)	24 (28.5)	
.6) 37	7 (2.6)	3 (3.8)	
47.9) 68	82 (47.9)	41 (47.9)	
			0.47
63.2) 89	94 (62.7)	60 (70.6)	
10.0) 14	43 (10.0)	8 (8.9)	
7.4) 10	05 (7.4)	6 (6.9)	
19.5) 28	83 (19.9)	12 (13.5)	
(73.6) 10	020 (73.2)	68 (81.4)	0.09
			0.04
46.7) 60	06 (47.5)	25 (34.2)	
27.3) 34	48 (27.2)	22 (28.9)	
26.0) 32	24 (25.3)	28 (36.9)	
		50 (50 1)	
55.9) 79	94 (55.8)	50 (58.1)	0.68
(((46.7) 6 (27.3) 3 (26.0) 3	(73.6) 1020 (73.2) (46.7) 606 (47.5) (27.3) 348 (27.2) (26.0) 324 (25.3)	(73.6) 1020 (73.2) 68 (81.4) (46.7) 606 (47.5) 25 (34.2) (27.3) 348 (27.2) 22 (28.9) (26.0) 324 (25.3) 28 (36.9)

*Chi square test p < 0.05 for the difference between the PCOS and no PCOS groups

PCOS: Polycystic ovary syndrome, BMI: body mass index

tistical tests include Pearson's chi-square test and Fisher's exact for significance.

differences in the sociodemographic characteristics of women who reported PCOS when compared with those who did not, however women with PCOS tended to be older (p = 0.07) and were more likely to have been pregnant (p = 0.09) (Table 1).

Women with PCOS had significantly higher BMI (mean BMI: 29.8 ± 8.7 vs. 26.8 ± 6.4 kg/m², p = 0.005), hence were more likely to be overweight or obese (p = 0.03). Prevalence of PCOS was higher amongst women who were overweight (5.9%, 95% CI 3.9-8.8) and obese (7.9%, 95% CI 5.5-11.2%) (p = 0.005) compared to normal weight) (5.4%, 95% CI 3.1-6.6). Women with PCOS were also more likely to be current smokers (p = 0.04).

The prevalence of PCOS peaked in the 35 to 44 year age group at 9.1% (95% CI 6.0–13.4%) and was lowest in those aged \geq 65 years (3.7%, 95% CI 2.1-6.2%) (Fig. 1).

Among women aged 15 to 44 years, those with PCOS were more likely to report diabetes, cardiovascular disease, and arthritis (all p < 0.05) (Table 2). These differences were not significant for women aged 45 years and over, however in this age group women with PCOS tended to report more diabetes, more asthma and more clinical depression symptoms than their non-PCOS peers.

Table 3 compares the risk of comorbidities and fair/poor selfassessed health among women who reported PCOS overall and those who did not.

Women with PCOS had a doubling in odds of diabetes (19.0% vs. 8.2%, adjOR 2.23, 95% CI 1.49-4.31) and tripling in odds of cardiovascular disease (8.2% vs. 4.3%, OR 3.18, 95% CI 1.31, 7.68); both findings were robust to adjustment for age and BMI. The frequency of other comorbidities or poor/fair self-assessed health was not significantly different between groups.

DISCUSSION

Main findings

This study is one of the first contemporary community-based studies examining the diagnosis of PCOS and the health status of affected women across the lifespan from adolescence to post-menopause. We found the prevalence of diagnosed PCOS peaked in the 35-44 age group (9.1%), and was lowest in the youngest (15-24 years) and oldest (65 and over) groups. PCOS was associated with an increased risk of diabetes and cardiovascular disease, independent of BMI, however, the excess risk was diminished in women aged 45 years or more.

Self-reported PCOS 16 14 PCOS prevalence 12 10 % 8 6 4 2 0 15-24 (n=9) 25-34 (n=17) 35-44 (n=21) 45-54 (n=16) 55-64 (n=10) 65+(n=12)Age group (years)

Fig. 1. Prevalence of self-reported, doctor-diagnosed PCOS by 10-year age group.

		Aged 15-44 years			Aged \geq 45 years		
	No PCOS n (%)	PCOS n (%)	p- value	No PCOS n (%)	PCOS n (%)	p-value	
Health Conditions							
Diabetes			≤0.001			0.07	
Yes	25 (3.8)	8 (16.7)		92 (11.9)	8 (21.9)		
No	623 (96.2)	40 (83.3)		685 (88.1)	30 (78.1)		
Cardiovascular disease			0.01*			0.32*	
Yes	4 (0.6)	3 (6.3)		57 (7.4)	4 (10.7)		
No	644 (99.4)	44 (93.7)		719 (92.6)	34 (89.3)		
Blood pressure medication use		· · · · · · · · · · · · · · · · · · ·	0.33*			0.14	
Yes	15 (2.3)	2 (3.8)		284 (36.5)	9 (24.7)		
No	633 (97.7)	47 (96.2)		493 (63.5)	28 (75.3)		
Cholesterol medication use			0.15*			0.76	
Yes	8 (1.2)	2 (3.7)		194 (25.0)	10 (27.2)		
No	640 (98.8)	47 (96.3)		583 (75.0)	28 (72.8)		
Current asthma			0.59			0.05	
Yes	109 (16.9)	9 (19.9)		129 (16.6)	11 (28.9)		
No	538 (83.1)	34 (80.1)		647 (83.4)	27 (71.1)		
Arthritis			0.04			0.49	
Yes	47 (7.2)	7 (15.5)		359 (46.4)	20 (52.2)		
No	601 (92.8)	40 (84.5)		415 (53.6)	18 (47.8)		
Clinical depression symptoms			0.84			0.08	
Yes	85 (13.2)	7 (14.2)		88 (11.3)	8 (20.6)		
No	562 (86.8)	41 (85.8)		688 (88.7)	30 (79.4)		
Anti-depressant use			0.20			0.59	
Yes	103 (16.0)	11 (23.1)		178 (23.0)	10 (26.7)		
No	544 (84.0)	36 (76.9)		598 (77.0)	28 (73.3)		
Self-reported health status							
Fair/poor			0.60			0.19	
Yes	55 (8.5)	5 (10.5)		170 (21.9)	12 (31.0)		
No	529 (91.5)	42 (89.2)		607 (78.1)	26 (69.0)		

Table 2. Physical, metabolic and psychological comorbidities and self-assessed health status in women reporting PCOS aged < 45 and \ge 45 years.

Pearson's chi square test p < 0.05, for the comparison of women self-reporting PCOS vs. those not reporting PCOS.

* Fisher's exact tes

adj: Adjusted, BP: blood pressure, PCOS: polycystic ovary syndrome, CI: confidence interval, OR: odds ratio.

Our findings suggest that there is under diagnosis of PCOS among younger and older women, as the clinical features of PCOS typically emerge around menarche (Ibanez et al., 2017) and many (e.g. elevated testosterone) persist as women age (Winters et al., 2000). Underdiagnoses in the younger cohort could reflect challenges in consensus criteria to diagnose PCOS in adolescents and/or the opinion that it is not appropriate to label girls with a diagnosis so early, but rather monitor them. Additionally, the older cohort would have been more likely to be diagnosed decades earlier during a time at which PCOS was less known or criteria more uncertain/controversial. Unfortunately, we did not have access to age of diagnosis so we can only speculate on this.

As we relied on self-reported, doctor-diagnosed PCOS, rather than participants being clinically examined, the peak in prevalence in women aged 35–44 years is likely to reflect diagnoses resulting from investigations and treatment for sub- and infertility (Lujan et al., 2008) (e.g. clinical guidelines recommend screening for ovulatory status in all infertility patients (Rasquin Leon & Mayrin, 2017)). This signals opportunities to improve diagnosis and awareness of PCOS outside of the reproductive years among both clinicians and women. Previous studies indicate that delays in PCOS diagnosis are common, with women often seeing more than three health professionals over a two-year period before a diagnosis is made (Gibson-Helm et al., 2017, 2014).

Interpretations

In our study, women with PCOS overall were more than twice as likely to report concurrent diabetes or cardiovascular disease, than women without PCOS, irrespective of BMI. However, when stratified by age group, the increased risk was most pronounced in women pre-menopause. For example, among women aged 45 years or more, there was no clear difference in the occurrence of cardiovascular disease between groups. These findings may suggest that women with PCOS experience an early onset of cardio-metabolic disease, however, the gap is reduced as women age, due to the deteriorating health of their peers. This is consistent with the limited existing

		OR (95% CI)				
	OR (95% CI)	p-value	adj for age*	p-value	adj for age and BMI*	p-value
Health conditions						
Diabetes	2.62 (1.48, 4.65)	0.001	3.08 (1.71, 5.56)	≤0.001	2.23 (1.49, 4.31)	0.018
Cardiovascular disease	2.01 (0.89, 4.53)	0.093	2.87 (1.21, 6.81)	0.017	3.18 (1.31, 7.68)	0.010
BP medication use	0.57 (0.29, 1.08)	0.082	0.73 (0.35, 1.50)	0.385	0.50 (0.23, 1.12)	0.091
Cholesterol medication use	0.99 (0.53, 1.87)	0.996	1.49 (0.73, 3.02)	0.274	1.33 (0.63, 2.83)	0.460
Current asthma	1.56 (0.93, 2.61)	0.093	1.55 (0.92, 2.60)	0.098	1.41 (0.80, 2.47)	0.233
Arthritis	1.17 (0.73, 1.87)	0.524	1.63 (0.96, 2.78)	0.073	1.41 (0.78, 2.55)	0.251
Clinical depression symptoms	1.48 (0.82, 2.66)	0.189	1.45 (0.80, 2.60)	0.219	1.34 (0.70, 2.56)	0.372
Anti-depressant use	1.33 (0.80, 2.22)	0.271	1.35 (0.81, 2.25)	0.246	1.19 (0.69, 2.08)	0.525
Self-reported health status						
Fair/poor health	0.76 (0.44, 1.33)	0.338	0.69 (0.39, 1.21)	0.192	0.93 (0.49, 1.74)	0.817

Table 3. Risk of physical, metabolic and psychological comorbidities and fair/poor self-assessed health among women reporting PCOS.

adj: Adjusted, PCOS: polycystic ovary syndrome, BMI: body mass index, BP: blood pressure, CI: confidence interval, OR: odds ratio.

* Age and BMI were continuous variables in the regression models.

** Rating dichotomised into excellent, very good or good vs. fair or poor.

research demonstrating there is no difference in mortality from cardiovascular disease between women with or without PCOS (Wild et al., 2000). Alternatively, while speculative, it is possible that risk is mitigated in older women with PCOS (who in our study are likely to have had severe symptoms of PCOS resulting in a diagnosis), as a result of improved health literacy and access to lifestyle intervention in mid to late life as part of PCOS care.

Our findings are an important expansion to the existing literature on the impact of PCOS, as while many studies report an increased frequency of risk factors for cardiovascular disease (e.g. obesity, dyslipidaemia, hypertension, etc.), few have examined established disease (Carmina, 2009). Further research, including longitudinal studies in unselected populations, is needed to understand the longterm consequences of PCOS.

In this study, women aged <45 years with PCOS were more likely to report a concurrent diagnosis of arthritis than their peers. While we are not aware of any previous reports of this association, it is plausible that inflammation, and/or lack of exercise, linked to obesity in PCOS could contribute to an increased risk of arthritis. This requires confirmation in future studies, and could identify new opportunities to improve the management of this condition.

In our study, approximately 20% of women with self-reported PCOS were current smokers, compared to 12% of women who did not report PCOS. These findings are inconsistent with another Australian community-based study, which reported no difference in smoking rates between women with or without PCOS (Htet et al., 2017; Moran et al., 2017). However, these studies were restricted to women aged between 28 to 36 years, coinciding with the peak reproductive years, which may underestimate the extent of smoking as life experiences such as starting a family can be a strong impetus to cease smoking (Fingerhut et al., 2010).

Overall, we found no differences between women with and without PCOS in terms of mental health (symptoms of clinical depression, use of antidepressants) and self-reported health status. This is in contrast to prior studies in clinical populations reporting lower self-reported health (Jones et al., 2008) and depression (Deeks et al., 2011). However, older women with PCOS tended to report more clinical symptoms of depression than their similarly aged peers who had not been diagnosed with PCOS (of borderline statistical significance). While this requires confirmation, these findings underscore the importance of psychological support for women with this condition.

Strengths

The strengths of this study include use of an established, rigorous sampling framework that is community based, includes women across the lifespan, and results a study sample that is broadly representative of the female population aged 15 or more in South Australia. The use of this survey as a data collection vehicle provides a wider age group than previous Australian studies on PCOS. This overcomes the major bias of many existing studies of PCOS that are based on infertile clinical populations. Indeed in this study the overall prevalence of PCOS was 5.6%, which is highly consistent with self-reported prevalence in other community-based cohorts in Australia (Joham et al., 2015; March et al., 2010) and internationally (Azziz et al., 2004; Michelmore et al., 1999; Nikokavoura et al., 2015).

Limitations

The study was limited by reliance on self-reported PCOS status, which, as discussed above, may underestimate prevalence due to the high number of women with PCOS who have not been diagnosed (March et al., 2010; Sivayoganathan et al., 2011). We were unable to ascertain which PCOS criteria was used for each woman's diagnosis. Older women, particularly those aged 65 and over may have also found it difficult to remember about a diagnosis, possibly introducing recall bias. In addition, investigations of lifestyle risk factors and comorbid conditions stratified by PCOS status and by age were underpowered to detect small but clinically meaningful differences due to small cell sizes, and should be interpreted with caution. Whilst it may have been ideal to have medical records of diagnoses of comorbidities it was beyond the scope of the current study. Imprecision may have influenced some outcomes, for example women were asked if they took antidepressants, and clinical depression was calculated using the MCS of the SF12, rather than completing a clinical assessment of mental health and wellbeing. However this survey has been validated in the Australian population for a number of different chronic conditions such as urinary incontinence (Avery et al., 2004, 2013, 2014), arthritis (Hill et al., 1999), asthma (Adams et al., 2001), sleep apnoea (Adams et al., 2012) and depression (Goldney et al., 2010).

ARTICLE

Implications for practice and/or policy

It is important to refer to agreed criteria for diagnosis of PCOS in adolescents, in order to avoid labelling of younger women, creating undue anxiety. Monitoring younger women is more appropriate. Further, an adequate diagnosis is necessary in order to encourage benefits from early lifestyle or medical interventions. Similarly, it is important to investigate new methods of diagnosis in older women, and consequently identify risk factors that may be more prevalent with PCOS throughout the Lifecourse.

CONCLUSION

Our community-based study provides important insights into the prevalence of PCOS and burden of comorbidities across the lifespan. Our findings point to under-diagnosis of this condition in younger and peri/post-menopausal women, and identify diabetes and CVD as key comorbidities requiring greater attention in younger women with PCOS. PCOS is underdiagnosed in younger and older women may be related to uncertainty of criteria in younger women/ adolescents as well as lack of awareness of PCOS by practitioners in decades prior, leading to lower diagnoses in women that have transitioned to the oldest cohort(s).

Improving timely diagnosis and management of this condition is critical, to ensure women receive the most benefit from early lifestyle and medical intervention to mitigate the significant risk of metabolic complications of PCOS.

ETHICS APPROVAL

The study design and survey questionnaire were approved by the University of Adelaide Human Research Ethics Committee (Approved 19/08/2015 Project No: H-097-2010).

CONSENT TO PARTICIPATE

Consent from participants was given when participants completed the survey.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors have no competing interests.

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AUTHORS' CONTRIBUTIONS

JCA is a Research Fellow, conceived the idea, undertook the analysis and drafted the manuscript and was also Project Manager of the South Australian Health Omnibus when the data was collected. AR assisted with the analysis and drafting of the manuscript. LM, RF, MW, MD and VM also assisted in the drafting of the manuscript. All seven authors edited and approved the paper.

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