Applied Epidemiology in Cardiovascular Disease and in COVID-19 in Queensland, Australia

A thesis submitted for the degree of Master of Philosophy in Applied Epidemiology of the Australian National University

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BSc, MBBS, MD, FRCP (UK), FRACP

June 2021

Field placement

Sunshine Coast University Hospital, Queensland Health, Birtinya, Queensland

Part funded by

National Heart Foundation of Australia Vanguard Grant

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Statement of authorship

I declare that the work contained in this thesis is my own work. To the best of my knowledge and belief this thesis contains no material previously published by another person except where due acknowledgement has been made. This thesis contains no material that has been accepted for the award of any other degree or diploma in any university. Contributions made to the research by others have been acknowledged in the respective chapter preface

Kim Greaves

June 2021

Acknowledgments

I dedicate this thesis to my dear father Professor Malcolm Watson Greaves (November 11th 1933- Jan 11th 2021) who sadly passed away in England before I could complete my degree. I am always grateful for his enthusiastic support over my career, and encouragement to undertake the MAE degree back in 2016. To my wonderful wife, Renee, whose steadying words re-centred me as to where the trees and forest were, when things sometimes felt a bit overwhelming – thank you. To my two children Michael and Mia, who are a constant source of happiness to me, and remind me to live in the moment – I feel blessed.

I would like to acknowledge and thank my two NCEPH supervisors Associate Professor Dr Rosemary Korda and Dr Jason Agostino who have opened my eyes up to the epidemiology of cardiovascular disease prevention. Dr Korda in particular, has spent many hours teaching me about epidemiology and I have thoroughly enjoyed the experience. We now work together on many projects and I hope this will continue after my degree! To both of my supervisors, I am most grateful.

I would also like to thank my field supervisor and work colleague Professor Tony Stanton. Cheers for being a great friend, colleague, personal therapist, and general supporter!

Finally, I would like to thank Professor Martyn Kirk who I managed to convince to allow me to undertake this degree, which has changed my working life for the better.

Abstract

Between February 2017 and June 2021, I undertook the Master of Philosophy in Applied Epidemiology at the Australian National University. During this period, I was employed as a cardiologist at the Sunshine Coast University Hospital, Birtinya, Queensland, a public hospital in Queensland Health. My thesis presents the results of the four required field research projects.

Acute Public Health Problem: *The ATHENA COVID-19 Study: Part 1 - data linkage study of outcomes in people diagnosed with COVID-19 in Queensland 1 January to 31 December 2020. Part 2: linkage of general practitioner (GP) data and consent-to-recontact.* The aim of Part 1 was to describe health outcomes and investigate predictors of outcomes for all people diagnosed with COVID-19 in Queensland by linking COVID-19 notification, hospital, general practice and death registry data. The aim of Part 2 was to establish a readily available and ongoing resource for access to COVID-19 patients' health care data and to the patient themselves, enabling biospecimen-related research including the study of long-COVID. The findings from Part 1 were consistent with what is known about COVID-19. This work reinforced the value of linking multiple data sources to enhance reporting of outcomes for people diagnosed with COVID-19 and provide a platform for longer term follow up. Part 2 demonstrated that the majority of COVID-19 patients are willing have their health care data, including that from general practices, used for research. They are also agreeable to being recontacted to discuss participation in COVID-19 related research. The ATHENA COVID-19 database will form a valuable future resource for research into COVID-19.

Evaluation of a Surveillance System: *The evaluation of Pen Computing System Population Aggregation Tool as a potential surveillance system for monitoring*

cardiovascular disease risk scores and appropriateness of treatment, for the Australian population. The Population Aggregation Tool Clinical Audit Tool (PAT CAT) produced by Pen Computing Systems, is widely available to Primary Health Networks across Australia, and has the capability to monitor cardiovascular disease (CVD) risk scores and treatment undertaken by GPs. This work 1) evaluated whether PAT CAT could be used as a surveillance system for monitoring absolute CVD risk scores and appropriateness of treatment 2) provided recommendations for improvement and 3) initiated actions to enable improvements.

Epidemiological Project: *A cross-sectional survey describing general practitioners' absolute cardiovascular disease risk assessment practices and their relationship to knowledge, attitudes and beliefs about cardiovascular disease risk in Queensland, Australia.* This study described GPs absolute cardiovascular disease risk (ACVDR) self-reported assessment practices and their relationship to knowledge, attitudes and beliefs about ACVDR. The findings were that although the majority of GPs report using the ACVDR calculator when undertaking an ACVDR assessment, there is a need to increase the actual proportion of eligible patients undergoing ACVDR assessment. This may be achieved by improving GP assessment practices such as GP and patient knowledge of cardiovascular disease risk, providing sufficient time and nurse-led assessment.

Data Analysis: *Prevalence of coronary microvascular dysfunction (CMD) in patients being investigated for chest pain in an outpatient setting, and association with typical angina symptoms: a cross-sectional study.* This project demonstrated that a third of patients referred to clinics with chest pain and normal coronary arteries have CMD. Global (whole of myocardium) CMD was not associated with typical angina but the

presence of CMD in the right coronary artery territory was associated with angina in both males and females. This strength of this association was similar in men and women.

In the thesis I also provide evidence of presentations conducted at national conferences and teaching exercises to colleagues.

Table of Contents

CHAPTER 1

INTRODUCTION

This introductory chapter outlines the activities undertaken for my degree. My background is that I am a consultant, general cardiologist with a specialist interest in cardiac imaging. I am employed full time at the tertiary centre, Sunshine Coast University Hospital, which is one of five hospitals that make up Sunshine Coast Hospital and Health Services, Queensland Health. The work for the MAE degree was undertaken between the periods of February 2017 to June 2021, and apart from the formal lecture modules held at the ANU itself, I carried out the whole of my degree on the Sunshine Coast region.

One main issue highlighted in this thesis is the intersection between public health, epidemiology and clinical practice, and the importance that their combination can have on informing and improving the delivery of health practice. For example, in Chapter 2, (Acute Public Health Problem) normally siloed health data (primary care, hospital and death data) on patients with COVID-19, are linked. This allowed for a more detailed assessment on the epidemiology of COVID-19 in Queensland, which in turn, was able to inform those working in the health sector on the best management for such an outbreak. In future, if this linkage set up became part of routine practice, this would be very helpful for the management of future outbreaks. Another intersection this thesis has highlighted is the importance of cardiovascular disease surveillance, and how it can feed into clinical practice.

Lessons learned are highlighted in more detail within each chapter, however to summarise I learnt how to manage larger projects and their teams, use STATA, the ethical issues and complexities around health data sharing, the importance of disease surveillance and the value of surveys.

Chapter 2 describes my investigation of an acute public health problem. This is related to COVID-19 and involves the linkage of the health care data sets of all patients infected with severe acute respiratory syndrome coronavirus 2 in Queensland from January 1st 2020 to Dec 31st 2020. The linked data allowed the provision of a descriptive profile for this cohort of patients.

Chapter 3 describes the evaluation of a surveillance system. The Population Aggregation Tool Clinical Audit Tool (PAT CAT) produced by Pen Computing Systems (Pen CS), is widely available to PHNs across Australia, and has the capability to monitor CVD risk scores and treatment. This chapter describes my evaluation of PAT CAT and a list of recommendations to be implemented to allow it to be used a surveillance system.

Chapter 4 describes the design and conductance of an epidemiological study. This is a cross-sectional study which involved the administration of a survey to over 100 general practitioners in Queensland. This then allowed us to provide a description of general practitioners' absolute cardiovascular disease risk assessment practices, and the relationship of these practices to GP's knowledge, attitudes and beliefs about cardiovascular disease risk.

Chapter 5 describes the analysis of a health data set. Chest pain is very common health problem, and makes up 6% of all health service presentations. The vast majority of patients with chest pain when investigated are found to have normal coronary arteries. Of these, a proportion are suggested to have coronary microvascular dysfunction as a cause of chest pain. We undertook a cross-sectional study to examine the prevalence of coronary microvascular dysfunction in patients being investigated for chest pain in an outpatient setting, and its association with typical angina symptoms.

Chapter 6 summarises and provides evidence of the other activities required for the MAE degree. These include reference to a targeted literature search with a review of the literature, and a report from one of the projects to a non-scientific audience (related to COVID-19). Also included are examples of papers published from the degree, presentations at national conferences, as well as the teaching of topics in field epidemiology.

At the end of the thesis, there is an Appendix which contains additional supportive material.

CHAPTER 2

ANALYSIS OF AN ACUTE PUBLIC HEALTH PROBLEM

The ATHENA COVID-19 Study - Part 1: Cohort profile and first findings for people diagnosed with COVID-19 in Queensland 1 January to 31 December 2020. Part 2: linkage of general practitioner data and consent-to-recontact.

Table of Contents Chapter 2

List of Figures and Tables

Abstract

Background To date, there are limited Australian data on characteristics of people diagnosed with COVID-19 and how these characteristics relate to outcomes. The ATHENA COVID-19 Study was established to describe health outcomes and investigate predictors of outcomes for all people diagnosed with COVID-19 in Queensland by linking COVID-19 notification, hospital, general practice and death registry data. It was also created to provide a readily available and ongoing resource for access to COVID-19 patients' health care data and to the patient themselves, enabling biospecimen-related research including the study of long-COVID. The aim of this paper was to report on the establishment and first findings for the ATHENA COVID-19 Study.

Methods The ATHENA COVID-19 Study was divided into two parts. Part 1 of the ATHENA COVID-19 Study used Notifiable Conditions System data from 1 January 2020 to 31 December 2020 linked to Emergency Department (ED) from 1 January 2020 to 31 December 2020) and Queensland Health Admitted Patient Data Collections (from 1 January 2010 to 30 January 2021) and Deaths Registrations data (from 1 January 2020 to 17 January 2021). Part 1 is complete and reported here. Part 2 at the time of writing, was in process of consenting patients and preliminary results are presented.

Results Up until 31 December 2020, 1254 people had been diagnosed with SARS-CoV-2 infection in Queensland; half were female (49.8%), two-thirds (67.7%) were aged between 20 and 59 years, and there was an over-representation of people living in less disadvantaged areas. More than half (57.6%) of people diagnosed presented to an ED, 21.2% were admitted to hospital as an inpatient (median length of stay 11 days), 1.4% were admitted to an intensive care unit (82.4% of these required ventilation) and there

were six deaths. Analysis of factors associated with these outcomes was limited due to small case numbers: people living in less disadvantaged areas had a lower risk of being admitted to hospital (test for trend, p<0.001), while those living in more remote areas were less likely than people living in major cities to present to an ED (test for trend: p=0.007), which may reflect differential health care access rather than health outcomes *per se*. Increasing age (test for trend, p<0.001) and being a current/recent smoker (age-sex-adjusted RR= 1.61, 95%CI: 1.00, 2.61) were associated with a higher risk of being admitted to hospital.

For Part 2 of the study, as of 27th May 2021, of the total cohort (1212) available for contacting, our project team had successfully contacted 896(87%). Of these, 655(73%) patients had reached a decision about consent, 474 (72%) had agreed to healthcare data release and recontact, and 181(28%) declined to participate. Of those who had agreed to participate in the study, 365(77%) patient healthcare data files had been received by the coordination centre from GPs. Patients are also being recontacted to participate in new research studies to examine host immune responses and genomics which predict adverse outcomes including long-COVID, and over 90% are agreeing to take part.

Conclusion Despite uncertainty in our estimates due to small numbers, our findings are consistent with what is known about COVID-19. Our findings reinforce the value of linking multiple data sources to enhance reporting of outcomes for people diagnosed with COVID-19 and provide a platform for longer term follow up. Part 2 also demonstrated that the majority of COVID-19 patients are willing have their health care data, including that from GPs, used for research. They are also agreeable to being recontacted to discuss participation in COVID-19 related research. Once recruitment is

completed, the ATHENA COVID-19 database will form a valuable future resource for research into COVID-19.

Keywords

COVID-19, Epidemiology, Outcomes, Predictors, Record Linkage, Surveillance, Morbidity

My role

I am the Principal Investigator and lead on ATHENA COVID-19 Project, taking overall responsibility. I conceptualised the idea and submitted a grant for funding to the Health Innovation Investment and Research Office at Queensland Health at the start of the pandemic. As chair of the Steering Committee and Data Linkage Committees I co-wrote the majority of and oversaw all protocols, patient information consent forms, fact sheets, ethics submissions, Public Health Act submissions, research governance submissions and telephone scripts manuscript write up and website (1). I oversaw the data linkage development, testing and data analysis and write up. My role involved the supervision of the different project streams and their individual project leads. The streams were:

ATHENA COVID-19 Coordination Centre: this was led by a general practitioner (Dr Zoltan Bourne) and had a team of 8 staff contacting patients and GPs to obtain consent and also for practices to send in individual patient files.

ATHENA COVID-19 Business Unit: this team of three led by a senior project officer (Mr Aaron Davies) from HIIRO was responsible for coordinating the whole project, ethics and research submissions, developing the electronic consent and managing funds.

ATHENA COVID-19 Data Linkage Team: this team was led by a senior IT project manager whose role was to develop the secure linkage systems, deidentification, and transfer of data from GP to our statistical services branch and onto our Data Analytics team at the Australian National University.

ANU Data Analytics team: Rosemary Korda and Jennifer Walsh

I did not undertake the data analysis myself as the ANU Data Analytics team was funded to undertake this by our group. However, I co-wrote the manuscript and the revisions required for its acceptance in Communicable Disease Intelligence, and I am the senior author.

Lessons learnt

I learnt better how to direct others, to let go and resist the temptation to micromanage. In a project of this size it was essential I devolve responsibility for set tasks to the project leads and trust that they would manage others, undertake tasks successfully, bring it in on schedule or notify me when there were problems. Regular contact with key members was also essential to keep me aware of what was going on. Being able to pick solid project leads to achieve this was also an important skill and I was lucky enough to have these. I learnt that IT teams that we pay to design and build the linkage for us, run on 'sprints' which are like buses, and if you miss them or are late, you have to wait for another one to come along - which sets your project back in time and often adversely affects other parts of the project. Also, if it's not in the initial 'Brief', IT will not adapt to any new requests unless you give them more funds. Research and innovation by definition, is not predictable and so this was costly. Finally, learning the skill to be able

to know when something is not right at Steering Committee meetings (despite not fully understanding the IT jargon) and calling it out.

Public health impact

The results of Part 1 informed senior health staff and executive in Queensland Health of epidemiology and outcomes of COVID-19 in Queensland. The manuscript for Part 1 has been accepted for publication in Communicable Diseases Intelligence. The ATHENA COVID-19 resource although complex to set up, is now an established resource and can be used to inform health service providers and researchers should there be another outbreak. Part 2 has demonstrated that the majority of those who have had COVID-19 are agreeable to releasing their health data for COVID-19 related research (including that from GP); that it is also possible to extract and link these data sets, and that 3rd party researchers are interested in using the resource created. The ATHENA-COVID-19-GENOMICS: host genetics and blood biomarker resource study (Professor Naomi Wray, Program Complex Traits Genomics, Institute for Molecular Bioscience, University of Queensland) is now underway. This study hypothesised that inter-individual differences in response to infection by COVID-19 are caused, in part, by genetic factors in the human host, as previously reported in other infectious diseases and that genetic susceptibility to COVID-19 involves many genes (similar to other complex diseases). Therefore, systematic assessment of genetic variants across the genome may reveal new and important insights. We have begun contacting those patients who have agreed to be recontacted to participate in the study.

Our group were approached by Queensland Health to be the first to test whether electronic consent (DocuSign) can be used as a means to consent research patients. This

was very successful and the vast majority of patients of all age groups found this easy to use. As a result, Queensland Health is intending to use DocuSign as means to consent patients for research. The success of the ATHENA COVID-19 concept has led to our team forming strong partnerships with other groups who are also interested in linking data nationally such as state health departments, research institutions, health data linkage groups, profession clinical organisations, community groups and clinical trial organisations/industry. Through this coalition we applied to the Medical Research Future Fund Frontiers grant program in December 2020, with Queensland health as the lead institution, and myself as the principal investigator. Unfortunately, this was unsuccessful, however, the process compelled us to define in greater detail the scope and costs of the project as well as pull together many different groups nationally together to support the program. Our team is now in the process of submitting a second MRFF grant – the Coronavirus Research Response in which we will use the ATHENA COVID-19 Project and the patient cohort collected, as the basis for this submission.

Acknowledgements

The ATHENA (Australians Together Health INitiAtive) COVID-19 Project Team which includes:

Health Innovation Investment and Research Office**:** Melissa Hagan, Helen Horton, Aaron Davies, Amanda King, Karen Thompson.

eHealth Queensland: Brendan Neill, Adrian Xavier, Tim Moffitt, Benson Choy, Rebecca Brownley, Gopi Sarawathi.

Steering Committee: Professor Mark Morgan, Dr Zoltan Bourne.

Queensland Health Statistical Services Branch: Trisha Johnston.

Notifiable Conditions Service: Ximena Toulousa.

Staff of the Epidemiology and Research Unit, Communicable Diseases Branch, Queensland Health for their invaluable assistance.

Funding

This project was funded by Health Innovation, Investment and Research Office (HIIRO), Queensland Health.

List of abbreviations

ATHENA	Australians Together HEalth INitiAtive
COVID-19	Coronavirus Disease 2019
ED	Emergency Department
EDC	Emergency Department Collection
GP	General practice
HIIRO	Health Innovation, Investment and Research Office
HREC	Health Service Human Research Ethics Committee
ICD	International Classification of Disease
ICU	Intensive Care Unit
IQR	Interquartile range
NoCS	Notifiable Conditions System
QHAPDC	Queensland Health Admitted Patient Data Collection
RR	Relative risk
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

Background

The novel coronavirus disease, named COVID-19 on 11 February 2020, is caused by the SARS-CoV-2 virus. It was first reported to the WHO Country Office in China on 31 December 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. As of 17 February 2021 there were over 108 million confirmed cases worldwide, with 2.4 million deaths [1]. Australia, partly due to successful contact tracing and isolation protocols, at the same time point has had only 28,905 confirmed cases and 909 deaths, and in Queensland 1,320 confirmed cases and 6 deaths [2].

Throughout the pandemic, international data has reported on the outcomes of people who test positive for SARS-CoV-2, and predictors of outcomes [3]. However, outcomes are likely to vary with context, including population profile, extensiveness of surveillance and testing and health system characteristics. Yet, there has been much less data available on characteristics and outcomes for people diagnosed with COVID-19 in Australia. One study of 204 patients admitted to intensive care units in Australia between 27 February and 30 June 2020 found that 69% were men and 64% had comorbidities (mostly obesity, diabetes, and chronic cardiac disease) [4]. People with chronic cardiac disease compared to those without were 3.4 times more likely to die in an intensive care unit (ICU). Another more recent study focussed on hospitalisation rates in cases of COVID-19 diagnosed in New South Wales between 1 January and 31 May 2020. However, with the exception of age and gender, no other health characteristics were reported or linked to outcomes [5].

Australian- and state-specific surveillance systems to monitor health outcomes and health service use is essential as the pandemic progresses. This paper describes the establishment and first findings from the Australian's Together Health Initiative

(ATHENA) COVID-19 Study, which was set up to enable ongoing investigation of health outcomes including service use, and predictors of outcomes, for all people diagnosed with COVID-19 in Queensland by linking COVID-19 notification, hospital, general practice and death registry data.

The ATHENA COVID-19 Study has two parts (see Methods section for detail). Part 1 links Queensland COVID-19 notification, hospital and death registry data and does not require informed consent (access was granted under section 282 of the Public Health Act 2005). Part 2 links Queensland COVID-19 notification, hospital and death registry data, as well as patient's healthcare information held within general practice, and requires patient consent.

The aims of the two parts of the ATHENA COVID-19 were as follows. Part 1 was set up to describe the health outcomes and investigate predictors of outcomes, for all people diagnosed with COVID-19 in Queensland by linking COVID-19 notification, hospital, general practice and death registry data. Part 2 was designed to further assess the strength of association between outcomes and sociodemographic and pre-existing health characteristics, using the additional more granular information gained from GP. For Part 2 additionally, as per a core concept of ATHENA, patients were also invited to give consent for re-contact by the project team to discuss participation in future unspecified but ethically-approved COVID-19-related research. The aim here was to create a cohort of patients who had had COVID-19 and establish a basis for additional important research that requires biospecimens, such as genomic analysis which are likely to play an important role in determining patient outcomes. An ATHENA COVID-19 Biobank has been created to house all biospecimens collected either as a matter of routine and for new investigator-led and industry sponsored clinical trials.

The results from both these studies could be used in models to predict outcomes, including effects on health services. Given the novelty and rapidly-changing nature of the epidemic, this data will also be of value for the international community.

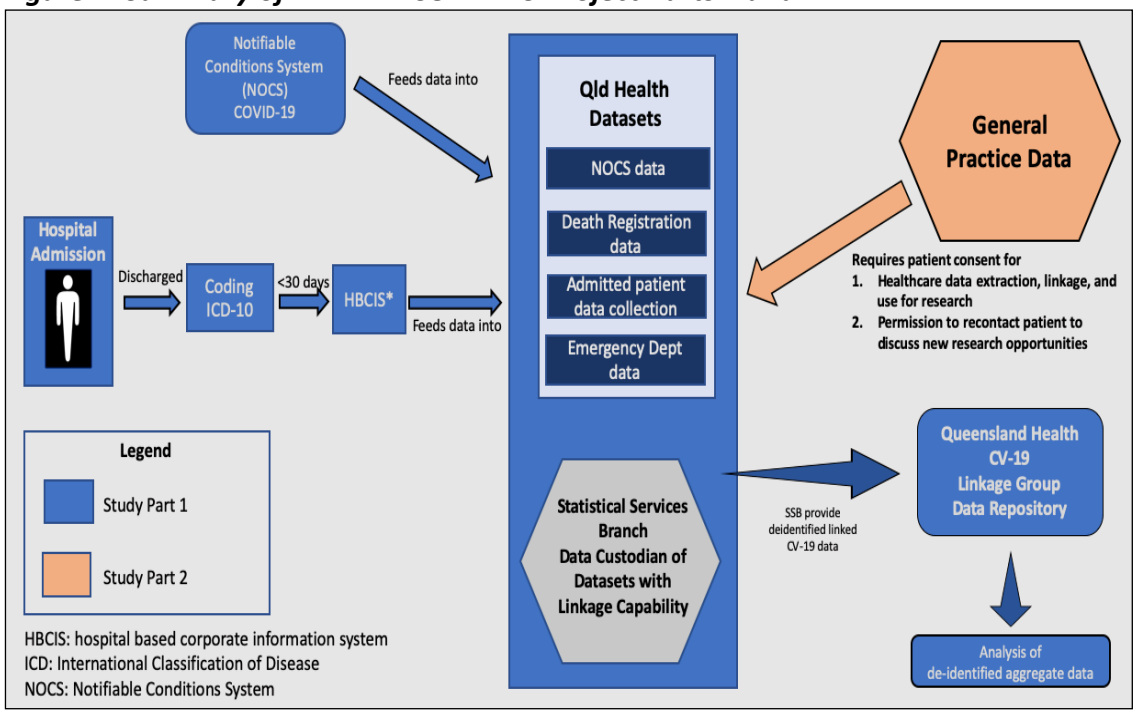
At the time writing, Part 1 has been completed and the results are presented here in full. For Part 2, at the time of writing, over half of the patient cohort had been contacted and approached for consent, and therefore only the methodology and limited results are given.

Methods

The Australian's Together Health Initiative (ATHENA) is a Queensland Health funded program involving the integration of primary, secondary and other healthcare data sets, using informed consent across Queensland. A proof-of-concept study was completed in June 2019 involving over 500 patients routinely attending two general practices. The principle purpose of this study was two-fold. Firstly, to assess the proportion of patients consenting to have their primary healthcare data extracted from their general practice into Queensland Health and linked to other data sets for ethically approved research. Secondly, to gain permission to recontact them in future to discuss clinical trial participation. 80% of patients consented to have both their data exported and linked, as well as recontact for trial participation. The successfully linked healthcare data was tested and found to be highly informative for clinical trial design and feasibility testing, as well as providing rapid access to large numbers of appropriate patients for real-world clinical trials. The ATHENA COVID-19 Study was opportunistically set up at the start of the pandemic using the same methods to create a cohort of all people diagnosed with COVID-19 in Queensland with linked primary, secondary and registry data (Figure 1).

These patients would be followed from recorded symptom onset date, to measure health service use and outcomes and to investigate predictors of these outcomes, as well as providing an ongoing resource for future clinical trial recruitment.

Figure 1. Summary of ATHENA COVID-19 Project Parts 1 and 2



Data

Part 1 of the ATHENA COVID-19 Study used routinely collected data from the Notifiable Conditions System (NoCS) for all people who tested positive for the SARS-CoV-2 virus in Queensland, linked to data from the Emergency Department Collection (EDC), Queensland Health Admitted Patient Data Collection (QHAPDC) and Deaths Registrations. The NoCS data (1 January 2020–31 December 2020) contained symptom onset date, sociodemographic characteristics and health outcomes. The EDC data (1 January 2020–31 December 2020) included emergency department (ED) arrival and departure dates and principal diagnosis. The QHAPDC data (1 January 2010–30 January 2021) contained admissions data from all public hospitals in Queensland, including admission and separation dates, and diagnosis codes. In Queensland, people diagnosed

with COVID-19 are only admitted to public hospitals. Death Registrations were available from 1 January 2020 to 17 January 2021. Data were linked probabilistically, using name, date of birth and address by the Statistical Services Branch within Queensland Health using established protocols [6].

Part 2 of the study, in addition to the routinely collected data as described in Part 1, also included GP patient data. GP patient health information was used to ascertain exposure information, include chronic health conditions (diabetes, cardiovascular disease, vaccination status, etc), health behaviours (e.g. smoking) and medication use for consented patients only. Further details on the variables can be found in the supplementary tables. For inclusion in Part 2, patients had to both test positive to the virus that causes COVID-19 (SARS-CoV-2) during the current pandemic, and, have 'consented' to share their GP health information for the purpose of this study. Study participants - confirmed cases of COVID-19 - were identified through the Notifiable Conditions Branch, using the NOCS data, from 1st Jan 2020 to 31st Dec 2020. Individual patients were then contacted by our call centre. We invited the participants to consent to the ATHENA COVID-19 Project and allow obtaining a copy of the participants' identifiable health information held within GP, to link and store it with their health information in Queensland Health. We also sought consent to use the combined health information for future as yet unspecified but ethically approved research related to COVID-19 research. 'Health information' was defined as patient health information held within GPs and hospitals, as well as biospecimens collected as part of routine clinical care for patients with COVID-19. Any initial and future contact would be carried out by a member of the ATHENA-COVID-19 Coordination Centre team whilst in operation, and in future by a member of the ATHENA COVID-19 Linkage Group led by an appointed Co-

Investigator. If the patient wished to participate in the new study, their contact details would be passed onto the specific research team for further discussions.

Sample

Our sample for this study included all people in Queensland who tested positive to the SARS-CoV-2 virus resulting in COVID-19 (n=1254), identified using NoCS data, from 1 January 2020- 31 March 2021 (referred to as the Queensland COVID-19 cohort). A confirmed case was defined according to the COVID-19 Series of National Guidelines and required laboratory definitive evidence of SARS-CoV-2 virus infection. Specifically, laboratory definitive evidence included: (1) detection of SARS-CoV-2 by nucleic amplification acid testing (NAAT); OR (2) isolation of SARS-CoV-2 in cell culture, with confirmation using a NAAT; OR (3) SARS-CoV-2 IgG seroconversion or a four-fold or greater increase in SARS-CoV-2 antibodies of any immunoglobulin subclass including 'total' assays in acute and convalescent sera, in the absence of vaccination [16].

Hospital-based outcomes and death

Our primary outcomes of interest were: presentations to an ED; inpatient admissions to a public hospital (which excluded virtual ward at home); admission to ICU; use of continuous ventilator support; and death. Secondary outcomes were time spent in: hospital; in ICU and on ventilation, as well as time between onset date and first hospital admission, and ICU admission and death.

Presentation to an ED was ascertained from the EDC data. ICU admissions (standard ward codes "ICU4", "ICU5" or "ICU6") and continuous ventilator support were ascertained from the linked QHAPDC data. We included ED presentations and hospital

admissions that occurred on or up to 6 weeks after symptom onset date, or where admission included date of onset.

Sociodemographic and health characteristics

Sociodemographic characteristics included age (in broad age groups), sex, remoteness (measured with Accessibility and Remoteness Index of Australia [ARIA+]), socioeconomic status (measured using Socio Economic Indexes for Areas, Index of Relative Disadvantage, [SEIFA IRSD], smoking status and health conditions, categorised as shown in Table 1.

ARIA+ is a geographical measure of service accessibility based on road distances to service centres (based on population size), which group areas into: major cities, inner regional, outer regional, remote, very remote areas [7]. SEIFA IRSD is an area-based measure of socioeconomic status, based on average characteristics of the people living within areas containing around 10,000 people [8].

Smoking status was obtained using information from all available QHAPDC records (i.e. prior to and after onset date, noting that collection of smoking status began on 1 July 2015 and was not recorded for virtual ward home admissions). People were categorised as a non-smoker if all QHAPDC records indicated that they were not a current smoker, or as a current smoker or recent smoker if at least one of their QHAPDC records indicated that they were a current smoker, or otherwise as missing (i.e. virtual QHAPDC records).

Comorbid conditions were identified using QHAPDC records in the 10 years prior to onset date, and measured with International Statistical Classification of Disease and Related Health Problems Version 10 (ICD-10-AM) codes. We also used QHAPDC data to

measure the Elixhauser comorbidity index, a validated measure involving 30 chronic health conditions [9], categorised as 0, 1, or 2+ conditions or "no hospital record prior to infection". The Elixhauser co-morbidity index is a method of categorising comorbidities of patients based on their ICD diagnostic codes and, using a weighting algorithm can predict hospital outcomes including mortality. Two separate categories were chosen to represent 'no hospital record prior to infection' and '0 comorbidities' because an absence of hospital record does not necessarily equate to an absence patient of comorbidities. Patients may have a history of medical disease yet never had contact with Queensland Health, the state's public health system, either because the disease was never severe enough to require hospital admission or the patient may have been managed in primary care, or been admitted to a public hospital outside of Queensland, and/or been managed in the private system.

Analysis

First we described the number and proportions of the cohort with each of the primary outcomes, as well as the median number of days (with interquartile range, IQR) in hospital and on continuous ventilator support. At the time of analysis, days spent in ICU were not available. We also cross-checked outcomes reported on the NoCS with outcomes derived from the linked data by comparing primary outcomes recorded in the hospital and death data with those reported using NoCS data. Third, we quantified the association between sociodemographic and health characteristics and two outcomes: presentation to an ED and inpatient admission to hospital. In this part of the analysis, although a person may have more than one presentation to an ED or admission to hospital (event), the outcome was defined as ever compared to never had the outcome.

We excluded ED presentations and hospital admissions where the first day of admission was more than 14 days after symptom onset to increase specificity of the estimates. We also excluded non-Queensland residents (n=61, defined as having a principal address outside of Queensland) to maximise the proportion with hospital admissions prior to infection being captured. To assess associations between comorbid health conditions and ED and inpatient hospital admissions, we compared those with the health condition to those without the condition with linked hospital records; those without linked hospital records prior to their onset date were categorised as missing. Associations were quantified with relative risks (RR) and 95% confidence intervals, estimated using Poisson regression, with adjustment for age, sex and region of residence. Where appropriate, we also performed tests for linear trend by including ordered categories as continuous terms in models.

We conducted two sets of sensitivity analyses. In the first, we re-estimated associations between comorbidities and hospital-based outcomes measuring comorbidities using all available QHAPDC data, i.e. additionally including admissions occurring after symptom onset date, to examine whether associations were similar when including diagnoses at the time of COVID-19-related admissions. In the second, we assumed that those without a hospital admission prior to their onset date did not have any of the measured comorbidities (previously excluded from the conditions analysis), including any of the comorbidities measured with the Elixhauser index (previously coded as a separate category)

Where possible, we report results stratified by sex and broad age group. Missing data were included as a separate category. All analyses were conducted using Stata version 16.0.

Initially when the study was being planned we were at the start of the pandemic and we undertook a power calculation expecting a sample of at least 3000 cases. However, there were only 1289 cases by Dec 1st 2021. The power calculation was therefore re-adjusted. Assuming a sample size of 1000 participants, 5% significance and 80% power, and a prevalence of the outcome in the reference group of 3%, the study was powered to detect odds ratios of 3.5, 2.7 and 2.3 for 5, 3 and 2 levels of exposure respectively. These detectable odds ratios fall to 2.8, 2.3 and 2.0, respectively, for outcomes with a prevalence of 5% in the reference group, and 2.2, 1.9 and 1.7 respectively for outcomes with a prevalence of 10% in the reference group. For rarer outcomes, e.g. proportion ventilated, which may be ~1%, we could only compare 2 exposure levels, in which case the study was powered to detect an odds ratio of 3.7.

Ethics approval

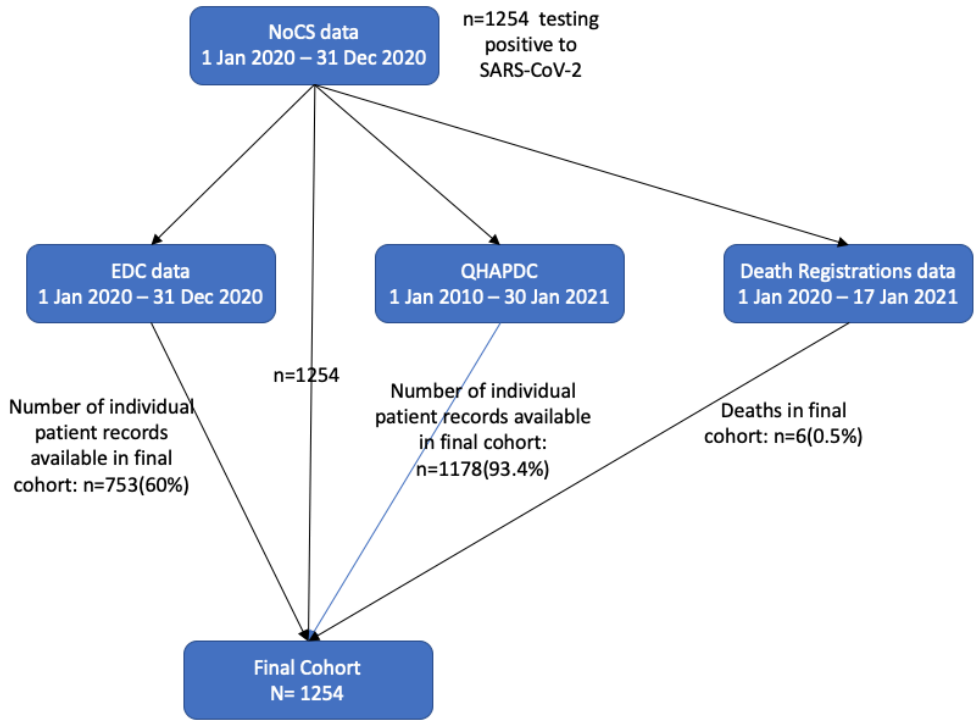
Ethics approval was granted by the Gold Coast Hospital and Health Service Human Research Ethics Committee (HREC/2020/QGC/63555); and the Australian National University Human Research Ethics Committee (2020/312). Informed consent was not required for this Part 1 of the study and access to de-identified data was granted under section 282 of the Public Health Act 2005 by the Director-General's delegate.

Results for Part 1

There were 1254 people that had a diagnosis of COVID-19 up to 31 December 2020. Of these, 753 (60.0%) linked to EDC data and most (n=1178, 93.4%) had a link to a QHAPDC record (since January 2010, 30,017 records). Out of the cohort, there were 288 inpatient hospital admissions among 267 (21.3%) patients, of whom 796 (63.5%) people had a QHAPDC record in the 10-years prior to onset date (3981 records). There were six deaths

in the linked Death Registrations dataset, consistent with the number of deaths reported by Queensland Health.

Figure 2. Flow chart of data inputs for Queensland COVID-19 cohort



NoCS: Notifiable Conditions System data: EDC: emergency Department Collection; QHAPDC: Queensland Health Admitted Patient Data Collections.

Characteristics of all people diagnosed with COVID-19 in Queensland

Two-thirds of people in the Queensland COVID-19 cohort were aged 20-<40 (38.7%) and 40-<60 (29.0%) years and half (49.8%) were women (Table 1). The majority (77.6%) were from major cities and a disproportionate number of cases were from the least disadvantaged areas (10.7% most disadvantaged, compared to 33.2% least disadvantaged, quintile). Smoking status was missing for a large proportion of the cohort (523, 41.7%), the majority were non-smokers (n=676, 53.9%) and a small proportion were recorded as a current/recent smoker (n=55, 4.4%).

For chronic health conditions captured in prior public hospital admissions, <2% of the cohort had a previous hospital admission with a diagnosis of asthma (1.0%), chronic lower respiratory disease (1.0%) or renal failure (1.5%). Almost 5% had recorded diabetes (4.2%), 6.0% cancer and 7.7% major cardiovascular disease (CVD). Most of the cohort (n=626, 49.9%) had none of the 30 comorbidities measured with the Elixhauser comorbidity index; 115 (9.2%) reported one comorbid condition, 55 (4.4%) reported two or more conditions, and 458 (36.5%) did not have a hospital record in the 10 years prior to infection.

Table 1. Characteristics of the Queensland COVID-19 Cohort (1 January 2020 to 31 December 2020)

	Men n (%)	**Women n (%)**	**Total n (%)**
Total	630 (50.2)	624 (49.8)	1254
Age groups			
0-<20 years	38 (6.0)	34 (5.4)	72 (5.7)
20-<40 years	214 (34.0)	271 (43.4)	485 (38.7)
40-<60 years	200 (31.7)	164 (26.3)	364 (29.0)
60-<75 years	138 (21.9)	132 (21.2)	270 (21.5)
75+ years	40 (6.3)	23 (3.7)	63 (5.0)
Accessibility and Remoteness Index of Australia (ARIA+)			
Major cities	483 (76.7)	490 (78.5)	973 (77.6)
Inner regional	67 (10.6)	66 (10.6)	133 (10.6)
Outer regional/ remote/ very remote	46 (7.3)	40 (6.4)	86 (6.9)
Non-Queensland resident	34 (5.4)	27 (4.3)	61 (4.9)
Index of Relative Socio-economic Disadvantage (SIEFA IRSD)			
Most disadvantaged quintile	66 (10.5)	68 (10.9)	134 (10.7)
2nd quintile	70 (11.1)	72 (11.5)	142 (11.3)
3rd quintile	116 (18.4)	100 (16.0)	216 (17.2)
4th quintile	134 (21.3)	150 (24.0)	284 (22.6)
Least disadvantaged quintile	210 (33.3)	206 (33.0)	416 (33.2)
Non-Queensland resident	34 (5.4)	27 (4.3)	61 (4.9)
Smoking status			
Non-smoker	316 (50.2)	360 (57.7)	676 (53.9)
Current/recent smoker	34 (5.4)	21 (3.4)	55 (4.4)
Missing	280 (44.4)	243 (38.9)	523 (41.7)
Elixhauser comorbidity measure			
0	283 (44.9)	343 (55)	626 (49.9)
1	56 (8.9)	59 (9.5)	115 (9.2)
2+	27 (4.3)	28 (4.5)	55 (4.4)
No hospital record prior to infection	264 (41.9)	194 (31.1)	458 (36.5)
Comorbid conditions			
Asthma	6 (1.0)	7 (1.1)	13 (1.0)
Chronic lower respiratory disease	5 (0.8)	8 (1.3)	13 (1.0)
Diabetes	30 (4.8)	23 (3.7)	53 (4.2)
Renal failure	11 (1.7)	8 (1.3)	19 (1.5)
Cancer	40 (6.3)	35 (5.6)	75 (6.0)
Cardiovascular disease	60 (9.5)	37 (5.9)	97 (7.7)

Notes: Sex, age, remoteness and SEIFA IRSD were sourced or derived from the NoCS data. Smoking status and comorbidities were obtained from QHAPDC data prior to onset date. SEIFA IRSD was measured in population-based quintiles. Smoking status was only recorded from 1 July 2015 and was not recorded for virtual ward home admissions. Asthma (ICD-10-AM: J45), chronic lower respiratory conditions excluding asthma (ICD-10-AM: J40-J47, excluding J45), diabetes (ICD-10-AM: E10-E14), renal failure (ICD-10-AM: N17-N19), cancer (ICD-10-AM: C00-C97), and major atherosclerotic/

thromboembolic cardiovascular disease (using established methods [10]: selected hypertensive diseases I11-I13; ischaemic heart disease I20-I25; pulmonary heart disease and diseases of pulmonary circulation I26-I28; other forms of heart disease I34-36, I42, I44, I46-I51; cerebrovascular disease I61-I67, I69; selected diseases of the arteries, arterioles and capillaries I70-I77; phlebitis and thrombophlebitis I80; and selected episodic and paroxysmal disorders G45, G46).

Outcomes for people diagnosed with COVID-19 in Queensland

There were 1182 people in the cohort that had an onset date before 1 November 2020 (Table 2). The median number of days between symptom onset date and first hospitalisation was 4 (IQR: 2-7 days) and once admitted, median length of stay was 11 days (IQR: 8-16). A greater proportion of the cohort ≥60 years had an inpatient hospital admission compared to those < 60 years (29.9% compared to 18.1%). 17 (1.4%) members of the cohort with onset before 1 November 2020 were admitted to ICU, 14 (1.2%) required ventilation and 6 (0.5%) died. Small numbers experiencing these outcomes precluded any further analyses. The NoCS data recorded that 337(29%) patients were hospitalised, 752(64%) were not hospitalised and no record was available in 93(8%). By comparison, the QHAPDC stated that 250(21%) patients required inpatient hospital admission, an additional 714(60%) were home-based admissions, and 218(18%) had no hospital record (Table A1, supplementary tables). The NoCS data recorded that 16 patients were admitted to ICU, and that 12 required ventilation, which was lower than the numbers recorded in the QHAPDC data (Tables A2 and A3, supplementary tables). A large proportion of NoCS data pertaining to patient hospitalisation, ventilation, admission to ICU and death was not recorded (Table A4, supplementary tables).

Table 2. Health outcomes for confirmed COVID-19 cases in Queensland (with onset before November 2020) through the Notifiable Conditions Systems (NoCS) data.

	Men	Women	Total
Total, n			
Presented to emergency department, n (%)	329 (56)	352 (59.2)	681 (57.6)
Inpatient hospital admission, n (%)	135 (23)	115 (19.3)	250 (21.2)
Length of stay (days), median (IQR)	12 (8-17)	11 (7-15)	11 (8-16)
Days from onset and hospitalisation, median (IQR)	4 (2-7)	5 (3-8)	4 (2-7)
Admitted to ICU, n (%)	n/a	n/a	17 (1.4)
Days between onset and ICU, median (IQR)	n/a	n/a	8 (6-10)
Required ventilation, n (%)	n/a	n/a	14 (1.2)
Days ventilated, median (IQR)	n/a	n/a	21 (11-35)
Died, n (%)	n/a	n/a	6 (0.5)
Days between onset and death, median (IQR)	n/a	n/a	11 (10-24)
Aged 0-<60 years, total n			
Presented to emergency department, n (%)	220 (53.4)	258 (58.2)	478 (55.9)
Inpatient hospital admission, n (%)	79 (19.2)	76 (17.2)	155 (18.1)
Aged 60+ years, total n			
Presented to emergency department, n (%)	109 (62.3)	94 (61.8)	203 (62.1)
Inpatient hospital admission, n (%)	56 (32)	39 (25.7)	95 (29.1)

Notes: Estimates are based on cohort members with an onset date prior to 1 November 2020 (n=1182). Emergency department admissions are measured with EDC data; hospital admissions, ICU and continuous ventilator support are measured with the QHAPDC, deaths are ascertained with the Death Registrations data. Inpatient hospital records exclude home-based admissions. Hospital data is yet to be finalised and these results should be considered preliminary. At the time of writing, data relating to length of stay in ICU was not available. Length of stay has been estimated excluding the 13 (7.1%) patients admitted and discharged on the same day. n/a indicates that the result has been suppressed because of cell size <5.

Over half (57.6%, n=681) of the cohort with onset date prior to 1 November 2020 presented to an ED in the six-week follow-up period. The majority (n=619, 90.9%) presented within two weeks of their symptom onset date. Proportions presenting did not vary substantially by broad age group (55.9% <60 years compared to 62.1% ≥60

years). Among those presenting to an ED, the most common primary diagnoses were COVID-19 (ICD-10: U07.1) and diagnoses related to viral and respiratory infections (Table 3). The 10 most common diagnoses accounted for almost 90% (89.2%) of all principle diagnoses among for those presenting to ED. Diagnoses were materially unchanged when restricted to presentations occurring within two weeks of recorded symptom onset date (see Table A5, supplementary tables).

Table 3. Top 10 principal diagnosis codes among COVID-19 patients presenting to an emergency department in Queensland.

Rank	ICD-10-AM code	Definition of ICD-10-AM code	n	%	Cumulative %
1	U07.1	Emergency use of U07.1	288	28.8	28.8
2	B34.9	Viral infection, unspecified	271	27.1	55.9
3	Z11.5	Special screening examination for other viral diseases	225	22.5	78.4
4	J06.9	Acute upper respiratory infection, unspecified	36	3.6	82.0
5	B34.2	Coronavirus infection, unspecified site	29	2.9	84.9
6	Z09.9	Follow-up examination after unspecified treatment for other conditions	12	1.2	86.1
7	R07.4	Chest pain, unspecified	8	0.8	86.9
8	J22	Unspecified acute lower respiratory infection	8	0.8	87.7
9	J11.1	Influenza with other respiratory manifestations, virus not identified	8	0.8	88.5
10	R50.9	Fever, unspecified	7	0.7	89.2

Note: Estimates are based on 998 admissions among 681 patients. Outcomes are measured with EDC data.

250 (21.2%) people in the COVID-19 cohort with onset before 1 November 2020 were admitted to hospital as an inpatient, and the majority (n=236, 94.4%) occurred within two weeks of recorded symptom onset date. Among those admitted to hospital, the

most common diagnoses were COVID-19, coronavirus, isolation, and symptoms associated with COVID-19, including cough, fever and headache (Table 4). However, the top 10 most common diagnoses accounted for less than half (47.9%) of all diagnoses among this patient cohort. Diagnoses were not materially different when restricted to admissions occurring within two weeks of recorded symptoms onset date (Table A6, supplementary tables).

Table 4. Top 10 principal diagnosis codes among COVID-19 patients requiring inpatient admission to hospital in Queensland.

Rank	ICD-10-AM code	Definition of ICD-10-AM code	n	%	Cumulative %
1	U07.1	COVID-19, virus identified	257	11.5	11.5
2	Z29.0	Isolation	234	10.5	22.0
3	B97.2	Coronavirus as the cause of disease classified to other chapters	216	9.7	31.7
4	R05	Cough	85	3.8	35.5
5	U82.3	Hypertension	51	2.3	37.8
6	R50.9	Fever, unspecified	50	2.2	40.0
7	Z86.43	Personal history of psychoactive substance abuse, tobacco use disorder	49	2.2	42.2
8	B34.2	Coronavirus infection, unspecified site	45	2.0	44.2
9	J128	Other viral pneumonia	41	1.8	46.1
10	R51	Headache	40	1.8	47.9

Notes: Estimates are based on 380 inpatient admissions among 250 patients. Outcomes are measured with data from the QHAPDC. U82.3 Hypertension is a supplementary code, assigned when a condition is present on admission but that does not meet the criteria for coding as instructed by the general and specialty coding standards, coding conventions, and coding rules.

Factors associated with a presentation to emergency or admission to hospital

There were 1148 people who were residents of Queensland with an onset date before 1 November 2020. Among these people, there was little variation in risks associated with presentation to an ED in relation to person characteristics after adjustment for age and sex (Table 5), apart from those residing in outer regional areas had lower risk of

presenting to an ED compared to those in major cities (age-sex-adjusted RR=0.64, 95%CI: 0.44, 0.92, test for trend: p=0.007). In age-sex-adjusted models, there was evidence that those in less disadvantaged areas had higher risks of presenting to an ED (test for trend, p=0.014), however this association was no longer evident after region was considered.

Table 5. Proportions and relative risks for emergency department presentation within two weeks of recorded symptom onset among Queensland residents with confirmed COVID-19 in relation to key sociodemographic characteristics

	Events/ persons (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Total	607/1148 (52.9)		
Age groups[#]			
0-<20 years	24/ 63 (38.1)	0.73 (0.48, 1.11)	0.72 (0.47, 1.09)
20-<40 years	226/ 432 (52.3)	1.00	1.00
40-<60 years	172/ 328 (52.4)	1.00 (0.82, 1.22)	1.01 (0.82, 1.23)
60-<75 years	148/ 264 (56.1)	1.07 (0.87, 1.32)	1.08 (0.88, 1.33)
75+ years	37/ 61 (60.7)	1.16 (0.82, 1.65)	1.18 (0.83, 1.68)
Sex[#]			
Men	300/ 566 (53.0)	1.00	1.00
Women	307/ 582 (52.7)	1.00 (0.85, 1.18)	1.00 (0.85, 1.17)
Accessibility and Remoteness Index of Australia (ARIA+)			
Major cities	516/ 935 (55.2)	1.00	-
Inner regional	60/ 127 (47.2)	0.83 (0.64, 1.09)	-
Outer regional/ remote	30/ 85 (35.3)	0.64 (0.44, 0.92)**	-
Index of Relative Socio-economic Disadvantage (IRSD)			
Most disadvantaged quintile	56/ 127 (44.1)	1.00	1.00
2nd quintile	62/ 141 (44)	0.97 (0.67, 1.39)	1.03 (0.71, 1.48)
3rd quintile	105/ 199 (52.8)	1.19 (0.86, 1.65)	1.19 (0.85, 1.67)
4th quintile	152/ 277 (54.9)	1.25 (0.92, 1.69)	1.20 (0.86, 1.66)
Least disadvantaged quintile	231/ 403 (57.3)	1.32 (0.98, 1.77)*	1.25 (0.92, 1.71)
Smoking status			
Non-smoker	357/ 613 (58.2)	1.00	1.00
Current/recent smoker	26/ 45 (57.8)	1.00 (0.67, 1.50)	1.00 (0.67, 1.49)
Missing	224/ 490 (45.7)	0.80 (0.68, 0.95)	0.78 (0.66, 0.93)
Elixhauser comorbidity measure			
0	326/ 612 (53.3)	1.00	1.00
1	64/ 113 (56.6)	1.03 (0.78, 1.36)	1.04 (0.79, 1.36)
2+	28/ 54 (51.9)	0.93 (0.63, 1.38)	0.95 (0.64, 1.41)
No hospital record	189/ 369 (51.2)	0.99 (0.82, 1.19)	0.98 (0.82, 1.18)
Comorbid conditions[±]			
Asthma	8/ 12 (66.7)	1.28 (0.64, 2.59)	1.24 (0.61, 2.51)
Chronic lower respiratory disease	9/ 13 (69.2)	1.22 (0.63, 2.40)	1.21 (0.61, 2.36)
Diabetes	34/ 52 (65.4)	1.18 (0.82, 1.70)	1.22 (0.84, 1.76)
Renal failure	11/ 19 (57.9)	1.03 (0.56, 1.89)	1.03 (0.56, 1.89)
Cancer	37/ 73 (50.7)	0.88 (0.62, 1.25)	0.88 (0.62, 1.25)
Cardiovascular disease	54/ 97 (55.7)	0.98 (0.73, 1.33)	1.00 (0.74, 1.36)

Notes: Estimates are based on 1148 people who were residents of Queensland with an onset date before 1 November 2020 and 607 presentations to emergency departments, measured with EDC data. Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex and remoteness, measured with ARIA+. [#]Where age is the primary exposure variable, Model 1 is adjusted only for sex. Where sex is the primary exposure variable, Model 1 is adjusted for only age. EDC data is yet to be finalised and results should be

*considered preliminary. ±Risks associated with comorbid conditions are estimated for each condition separately, using those with a hospital record but without the condition as the reference category. * indicates that the test for linear trend was significant, p<0.05, ** p<0.01. Age, sex, remoteness and SEIFA IRSD are measured with or derived from NoCS data. Smoking status and comorbidities are measured with QHAPDC prior to onset date. SEIFA IRSD is measured in population-based quintiles.*

Proportions admitted to hospital increased with age (<20% of those <40 years to >34% aged ≥75 years), being a current/recent smoker (42.2%) compared to non-smokers (27.9%), and having a comorbid chronic health condition (26.3-38.5% compared with no comorbid condition (18.8%). There was considerable uncertainty in the estimates in the age-sex-adjusted models. However, risk of hospital admission increased with greater age (test for linear trend: p<0.001) and was elevated among current/recent smokers compared to non-smokers (age-sex-adjusted RR=1.62, 95%CI: 1.00, 2.61); those living in less disadvantaged areas had lower risk of being admitted to hospital (age-sex-adjusted test for trend, p=0.001) (Model 1, Table 6). There was no material difference in these results after adjustment for region (Model 2, Table 6).

Table 6. Proportions and relative risks for an inpatient admission to hospital within two weeks of recorded COVID-19 symptom onset among Queensland residents in relation to key sociodemographic characteristics

	Events/ persons (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Total	227/ 1148 (19.8)		
Age group[#]			
0-<20 years	11/ 63 (17.5)	1.13 (0.60, 2.14)	1.18 (0.62, 2.23)
20-<40 years	66/ 432 (15.3)	1.00	1.00
40-<60 years	61/ 328 (18.6)	1.19 (0.84, 1.69)	1.19 (0.84, 1.69)
60-<75 years	68/ 264 (25.8)	1.66 (1.19, 2.34)	1.68 (1.19, 2.36)
75+ years	21/ 61 (34.4)	2.17 (1.32, 3.56) ***	2.20 (1.34, 3.63) ***
Sex [#]			
Men	124/ 566 (21.9)	1.00	1.00
Women	103/ 582 (17.7)	0.85 (0.65, 1.10)	0.86 (0.66, 1.11)
Accessibility and Remoteness Index of Australia (ARIA+)			
Major cities	171/ 935 (18.3)	1.00	-
Inner regional	28/ 127 (22)	1.08 (0.72, 1.62)	-
Outer regional/ remote	28/ 85 (32.9)	1.83 (1.22, 2.73) **	-
Index of Relative Socio-economic Disadvantage (IRSD)			
Most disadvantaged quintile	45/ 127 (35.4)	1.00	1.00
2nd quintile	38/ 141 (27)	0.74 (0.48, 1.15)	0.70 (0.45, 1.08)
3rd quintile	46/ 199 (23.1)	0.67 (0.45, 1.02)	0.60 (0.39, 0.92)
4th quintile	56/ 277 (20.2)	0.60 (0.40, 0.89)	0.55 (0.36, 0.83)
Least disadvantaged quintile	42/ 403 (10.4)	0.32 (0.21, 0.48) ***	0.30 (0.19, 0.46) ***
Smoking status			
Non-smoker	171/ 613 (27.9)	1.00	1.000)
Current/recent smoker	19/ 45 (42.2)	1.62 (1.00, 2.61)	1.61 (1.00, 2.61)
Missing	37/ 490 (7.6)	0.27 (0.19, 0.39)	0.28 (0.19, 0.40)
Elixhauser comorbidity measure			
0	115/ 612 (18.8)	1.00	1.00
1	30/ 113 (26.5)	1.22 (0.81, 1.84)	1.21 (0.80, 1.82)
2+	15/ 54 (27.8)	1.21 (0.70, 2.10)	1.20 (0.69, 2.08)
No hospital record	67/ 369 (18.2)	1.03 (0.76, 1.41)	1.03 (0.76, 1.41)
Comorbid conditions[±]			
Asthma	<5/ 12 (<42.0)	1.15 (0.37, 3.63)	1.22 (0.39, 3.84)
Chronic lower respiratory disease	5/ 13 (38.5)	1.47 (0.59, 3.66)	1.54 (0.62, 3.85)
Diabetes	16/ 52 (30.8)	1.18 (0.69, 2.01)	1.23 (0.66, 1.94)
Renal failure	5/ 19 (26.3)	1.00 (0.41, 2.46)	1.04 (0.42, 2.57)
Cancer	20/ 73 (27.4)	1.07 (0.66, 1.75)	1.08 (0.66, 1.77)
Cardiovascular disease	28/ 97 (28.9)	1.13 (0.74, 1.75)	1.12 (0.73, 1.73)

Notes: Estimates are based on 1148 people who were residents of Queensland with an onset date before 1 November 2020 and 227 inpatient hospital admissions, measured with QHAPDC data. Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex and remoteness, measured with ARIA+. [#]Where age is the primary exposure variable,

*Model 1 is adjusted only for sex. Where sex is the primary exposure variable, Model 1 is adjusted for only age. QHAPDC data is yet to be finalised and results should be considered preliminary. ±Risks associated with comorbid conditions are estimated for each condition separately, using those with a hospital record but without the condition as the reference category. ** indicates that the test for linear trend was significant, p<0.01, ***p<0.001. Age, sex, remoteness and SEIFA IRSD are measured with or derived from NoCS data. Smoking status and comorbidities are measured with hospital data prior to onset date. SEIFA IRSD is measured in population-based quintiles.*

Sensitivity analyses

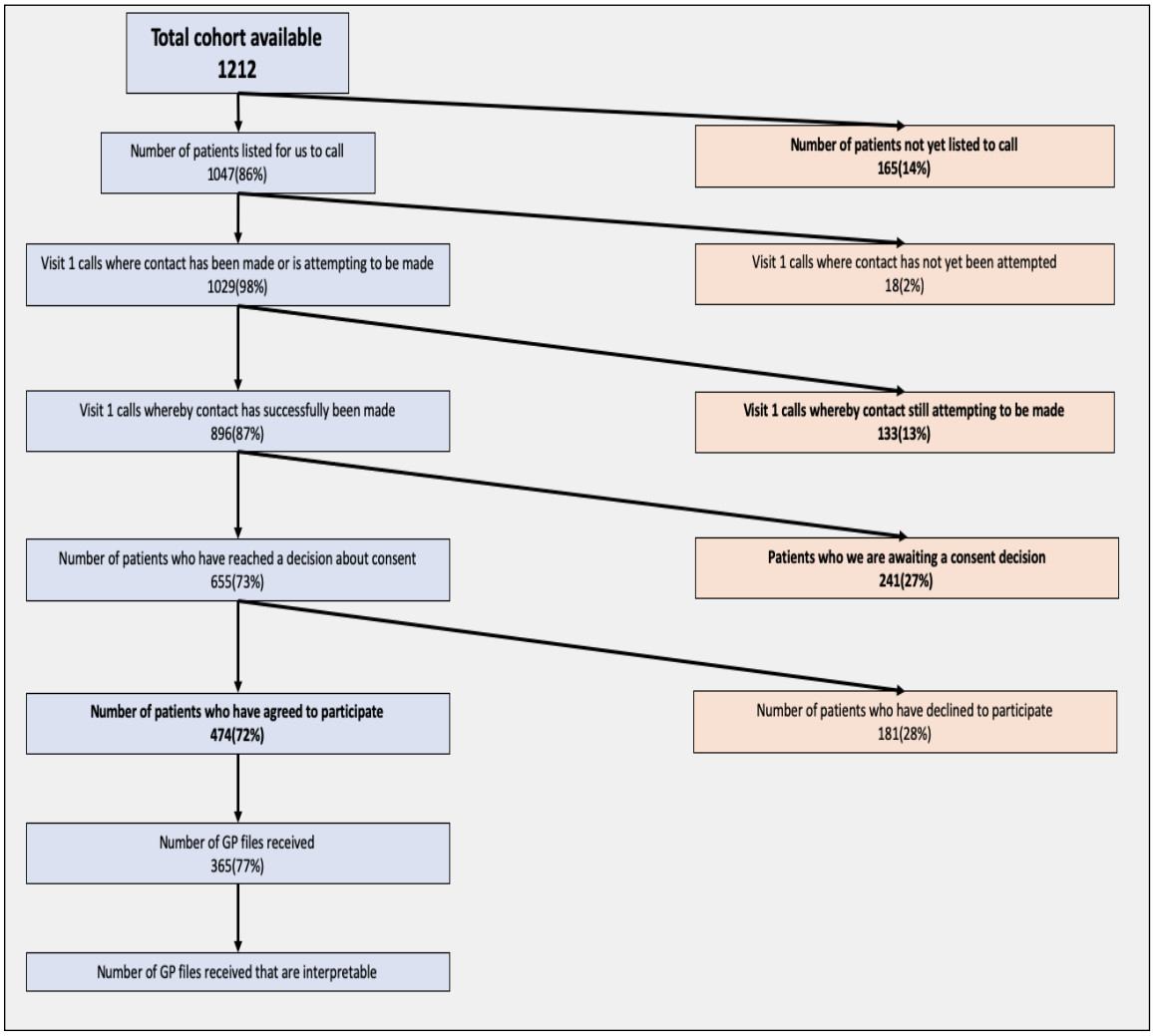
When comorbidities included those recorded in hospital admissions after symptom onset, proportions with each of the comorbid health conditions increased slightly (see supplementary tables, Table A7). Associations between comorbid health conditions and presentation to emergency (supplementary tables, Table A8) were substantially unchanged. Associations between comorbid health conditions and inpatient hospital admissions did not change materially, except that those with renal failure had higher risk of hospital admission compared to those without (age-sex adjusted RR= 1.75, 95%CI: 1.07, 2.86, supplementary tables Table A9). Some caution should be applied when interpreting these results, as health conditions measured at the time or after onset may be the outcome of COVID-19 rather than a pre-existing condition. Similarly, associations between comorbid conditions and outcomes were materially unchanged when assuming those without a hospital record prior to onset date had none of the measured comorbidities (supplementary tables, Tables A10-11).

Results for Part 2

For Part 2 of the study, as of 27th May 2021, of the total cohort (1212) available for contacting, our project team had successfully contacted 896(87%) contact (Figure 3). Of these, 655(73%) patients had reached a decision about consent, of whom 474 (72%) had

agreed to healthcare data release and recontact, and 181(28%) declined to participate. Of those had agreed to participate in the study, 365(77%) patient healthcare data files had been received by the coordination centre from GPs. Patients are also being recontacted to participate in new research studies to examine host immune responses and genomics which predict adverse outcomes including long-COVID, and 90% are agreeing to take part.

Figure 3. Flow diagram of patient recruitment to the ATHENA COVID-19 Study Part 2.



Discussion

By linking administrative data, we described the characteristics, hospital-based outcomes and deaths for all confirmed COVID-19 cases in Queensland, and the utility of using linked data for ongoing surveillance purposes as the pandemic continues. Over half of people diagnosed had at least one ED presentation; one in five had an inpatient hospital admission (median length of stay 11 days), 1.4% were admitted to ICU (majority requiring ventilation) and six died. Increasing age and being a smoker were associated with higher risk of admission while those in less disadvantaged areas had lower risk. There was some evidence that people with chronic health conditions had an elevated risk of being admitted, however small numbers limited the precision of our estimates.

Our finding that presentations to an ED were relatively common is consistent with Queensland policies regarding testing location during the pandemic. The majority of those diagnosed with COVID-19 in Queensland acquired the virus overseas and were likely in quarantine when symptoms became apparent [11]. EDs were the first point of contact for these people. Even those not in quarantine were discouraged from entering GP clinics if they reported any COVID-19 related symptoms, and were instead referred to their nearest ED. This policy remained in place even after State and Commonwealth Governments established fever clinics which would have reduced the number of patients presenting to an ED. The only characteristic we examined that was associated with lower risk of presenting to an ED was living in an outer regional area, likely reflecting reduced access to an ED.

Proportions of people diagnosed with COVID-19 experiencing adverse outcomes are likely to be dependent on a number of region-specific factors, including population profile, health system factors and the public health actions taken by individuals and

Government. Furthermore, international comparisons with people diagnosed with COVID-19 in Queensland are difficult given that most previous research examines outcomes among ED presentations, hospitalised COVID-19 patients and/or expresses outcomes as rates (rather than proportions) [12,13].

The associations between person characteristics and inpatient hospital admissions in the Queensland COVID-19 cohort were consistent with what is already known about adverse outcomes in people diagnosed with COVID-19. Previous research has found that increasing age, being a smoker and area-level deprivation are associated with adverse outcomes in people diagnosed with COVID-19 compared to uninfected members of the population, as are chronic health conditions such as respiratory disease (excluding asthma), cardiovascular disease, diabetes, recent cancer and reduced kidney function [14,15].

This project demonstrates the value of data linkage across health services to monitor outcomes and contribute to the international evidence on COVID-19. NoCS data whilst valuable, is limited by incomplete data records, the impracticability of collecting extra information such as co-morbidities and the time needed for long-term follow-up. Queensland Health already has a wide array of established data sets which contain valuable and additional health care information. Linking NoCS data to additional data sources – hospitalisations, emergency department and death data – enabled additional and complementary data for people with COVID-19 (including more complete outcome data), ultimately increasing the value of the NoCS data collected from case report forms. Furthermore, it allowed for ascertainment of hospital-based and death outcomes for all people diagnosed with COVID-19, which has been limited in many international settings to only those admitted to hospital. Having established the resource, the ATHENA COVID-

19 Study can now also be used a platform for monitoring longer-term outcomes. In order to both strengthen and increase the utility of existing notifiable disease surveillance systems against future pandemics, it would seem prudent to routinely establish the linkage capabilities between these different data bases.

Part 2 of the study, although not yet completed, confirms the previous findings of the GP Data Linkage study (in draft format) - that the majority of the public are willing to consent to provide their GP health information and other healthcare data sets for ethically-approved research. The same proportion of participants also agreed to participate in a pool of willing volunteers ready to help further medical research. Although the majority of cohort consented to participate, the proportion was lower than expected. It was expected that COVID-19 patients would have a vested interest in participating by finding successful treatments for COVID-19 and therefore that the proportion agreeing to participate would be higher than it was in the GP Data Linkage study, which was 80%. In addition to a further descriptive analysis of the COVID-19 cohort and predictors of outcomes, the GP data will also be: 1) assessed for data quality; 2) compared with the Queensland Health Data sets to assess what additional insights the data bring in comparison to the Queensland Health Data Sets. In addition, a report will be prepared describing the attitudes of participants, GPs and other stakeholders on sharing health care data and consent to recontact. There will also be an assessment of the secondary use of the ATHENA COVID-19 Database and Biobank by external researchers. However, it is already known that there are several projects planning to use the resource.

Our findings, particularly those regarding associations between pre-existing conditions and hospital outcomes, should be interpreted with data limitations in mind. Hospital

data were limited to Queensland public hospitals. There were no Queensland COVID-19-related admissions to private hospitals in Queensland or to hospitals outside the state, and hence, ascertainment of hospital outcomes is likely complete. However, our measure of comorbidities based on hospital data (in the 10 years prior to COVID-19 diagnosis) is likely incomplete given some cohort members may have been admitted to private hospital or to a hospital outside Queensland in the relevant period. There may also be missing data due to linkage error. Consequently, prevalence of these conditions will be underestimated, which may or may not have affected RR estimates of the associations between chronic conditions and inpatient hospital admission. The sociodemographic and health characteristics included were limited to the data that were available and other information, including more detail on health conditions and information on medications would have been useful. Discrepancies between the NoCS and QHAPDC data most likely reflect a combination of non-recorded data (NoCS) and no hospital record available (QHAPDC). That 93% rather than 100%, of COVID-19 patients had data linked to QHAPDC is likely due to the delay in virtual wards being set up. During this period, those patients who were asymptomatic or mildly ill would not have required admission to hospital and therefore would not have evidence of admitted data. It should also be noted that the definitions for confirmed, vs clinically diagnosed vs probable COVID-19 designed to capture patients COVID-19 presenting to emergency departments, changed over the course of the pandemic. This study used ICD-10-AM coding U07.1 to capture emergency department and hospital admissions rather than U07.2. The former requires laboratory confirmation whereas the latter is a clinical diagnosis usually used when testing is not available. Finally, reflecting the success that Queensland showed in curbing the pandemic, there were small numbers of COVID-19 cases in this study. This resulted in considerable uncertainty in estimates of association

between characteristics and outcomes, limiting our ability to examine factors predicting hospital-based outcomes.

The ATHENA COVID-19 Study is now an established resource. While Australia's success managing the pandemic has ensured cases have remained low since the peak of the pandemic in Queensland in late March, the ATHENA COVID-19 Study can be used for monitoring of COVID-19 outcomes should there be another wave or increased community transmission, as well as longer-term follow-up. Furthermore, the data could be aggregated with similar data from other Australian states and territories to increase their analytical power.

Supplementary material

Table A1. Number of cases with onset date before 1 November 2020 reported as being hospitalised in the Notifiable Conditions System data (NoCS) and the linked data from Queensland Health Admitted Patient Data Collection

		Queensland Health Admitted Patient Data Collection Data			
		No hospital record	Home-based admission	Inpatient hospital admission	Total
Notifiable Conditions System data	Not hospitalised	194	500	58	752
	Hospitalised	14	146	177	337
	Not recorded	10	68	15	93
	Total	218	714	250	1,182

Table A2. Number of cases with onset date before 1 November 2020 reported as requiring ventilation in the Notifiable Conditions System data (NoCS) and the linked data from Queensland Health Admitted Patient Data Collection.

		Queensland Health Admitted Patient Data Collection Data			
		No hospital record	Not ventilation	Required ventilation	Total
Notifiable Conditions System data	Not ventilated	40	217	<5	XXXX
	Required ventilation	<5	<5	<5	12
	Not recorded	177	733	<5	XXXX
	Total	XXXX	XXXX	14	XXXX

Table A3. Number of cases with onset date before 1 November 2020 reported as being admitted to an Intensive Care Unit (ICU) in the Notifiable Conditions System data (NoCS) and the linked data from Queensland Health Admitted Patient Data Collection

		Queensland Health Admitted Patient Data Collection Data			
		No hospital record	Not admitted to ICU	Admitted to ICU	Total
Notifiable Conditions System data	Not admitted to ICU	156	649	<5	XXXX
	Admitted to ICU	<5	<5	<5	16
	Not recorded	59	298	<5	XXXX
	Total	XXXX	XXXX	17	XXXX

Table A4. Number of cases with onset date before 1 November 2020 reported as having died in the Notifiable Conditions System data (NoCS) and the linked Death Registrations data.

		Death Registrations data		
		No record	Died	Total
Notifiable Conditions System data	Not recorded as having died	959	<5	XXXX
	Recorded as having died	<5	<5	6
	Not recorded	XXXX	<5	XXXX
	Total	XXXX	6	XXXX

Table A5 Top 10 principal diagnosis codes among COVID-19 patients presenting to an emergency department in Queensland within two weeks of recorded symptom onset date.

Rank	ICD-10-AM code	Definition of ICD-10-AM code	n	%	Cumulative %
1	B34.9	Viral infection, unspecified	236	31.9	31.9
2	U07.1	Emergency use of U07.1	191	25.8	57.7
3	Z11.5	Special screening examination for other viral diseases	167	22.6	80.3
4	J06.9	Acute upper respiratory infection, unspecified	31	4.2	84.5
5	B34.2	Coronavirus infection, unspecified site	28	3.8	88.2
6	J18.9	Pneumonia, unspecified	7	0.9	89.2
7	J11.1	Influenza with other respiratory manifestations, virus not identified	7	0.9	90.1
8	R50.9	Fever, unspecified	7	0.9	91.1
9	R07.4	Chest pain, unspecified	5	0.7	91.8
10	J22	Unspecified acute lower respiratory infection	5	0.7	92.4

Notes: Estimates are based on 740 presentations among 622 patients. Outcomes are measured with data from the QHAPDC.

Table A6. Top 10 principal diagnosis codes among COVID-19 patients within two weeks of recorded symptom onset date requiring inpatient admission to hospital in Queensland.

Rank	ICD-10-AM code	Definition of ICD-10-AM code	n	%	Cumulative %
1	U071	Emergency use of U07.1	240	11.7	11.7
2	Z290	Isolation	219	10.7	22.4
3	B972	Coronavirus	200	9.7	32.1
4	R05	Cough	77	3.8	35.8
5	U823	Hypertension	45	2.2	38.0
6	R509	Fever	45	2.2	40.2
7	B342	Coronavirus infection unspecific site	43	2.1	42.3
8	Z8643	Personal history of psychoactive substance abuse, tobacco use disorder	43	2.1	44.4
9	J128	Other viral pneumonia	40	1.9	46.4
10	R51	Headache	35	1.7	48.1

Notes: Estimates are based on 1065 inpatient admissions among 938 patients. Outcomes are measured with data from the QHAPDC. U82.3 Hypertension is a supplementary code, assigned when a condition is present on admission but that does not meet the criteria for coding as instructed by the general and specialty coding standards, coding conventions, and coding rules.

Table A7. Proportions of confirmed COVID-19 cases with comorbid chronic health conditions, measured using all available QHAPDC records.

	Men n (%)	Women n (%)	Total n (%)
Asthma	16 (2.5)	22 (3.5)	38 (3.0)
Chronic lower respiratory disease	10 (1.6)	9 (1.4)	19 (1.5)
Diabetes	43 (6.8)	30 (4.8)	73 (5.8)
Renal failure	28 (4.4)	12 (1.9)	40 (3.2)
Cancer	40 (6.3)	35 (5.6)	75 (6.0)
Circulatory disease	73 (11.6)	40 (6.4)	113 (9.0)

Estimates are based on all 1254 cohort members.

Table A8. Crude and age-sex-adjusted risks for emergency department presentation among Queensland residents with confirmed COVID-19 in relation to comorbid conditions, including QHAPDC records post COVID-19 onset.

	Events/ persons (%)	Age-sex-adjusted RR (95%CI)
Asthma	26/ 36 (72.2)	1.13 (0.76, 1.68)
Chronic lower respiratory disease	15/ 18 (83.3)	1.25 (0.73, 2.14)
Diabetes	45/ 68 (66.2)	1.00 (0.72, 1.37)
Renal failure	27/ 39 (69.2)	1.05 (0.70, 1.56)
Cancer	44/ 73 (60.3)	0.88 (0.63, 1.22)
Circulatory disease	72/ 112 (64.3)	0.97 (0.74, 1.28)

Estimates are based on 1148 cohort members who were Queensland residents and had an onset date before 1 November 2020.

Table A9. Crude and age-sex-adjusted risks for inpatient hospital admission within 2 weeks of symptoms onset among Queensland residents with confirmed COVID-19 in relation to comorbid conditions, including QHPADC records post COVID-19 onset.

	Events/ persons (%)	Age-sex-adjusted RR (95%CI)
Asthma	11/ 36 (30.6)	1.32, (0.71, 2.45)
Chronic lower respiratory disease	9/ 18 (50.0)	1.65 (0.81, 3.36)
Diabetes	22/ 68 (32.4)	1.10 (0.69, 1.76)
Renal failure	20/ 39 (51.3)	1.75 (1.07, 2.86)
Cancer	20/ 73 (27.4)	0.91 (0.56, 1.48)
Circulatory disease	40/ 112 (35.7)	1.30 (0.88, 1.92)

Estimates are based on 1148 cohort members who were Queensland residents and had an onset date before 1 November 2020.

Table A10. Crude and age-sex-adjusted risks for emergency department presentation among Queensland residents with confirmed COVID-19 in relation to comorbid conditions, assuming patients with no QHAPDC records prior to onset had none of the measured comorbidities.

	Events/ persons (%)	Age-sex-adjusted RR (95%CI)
Asthma	9/ 12 (75.0)	1.31 (0.68, 2.53)
Chronic lower respiratory disease	11/ 13 (84.6)	1.36 (0.74, 2.50)
Diabetes	37/ 52 (71.2)	1.17 (0.83, 1.67)
Renal failure	12/ 19 (63.2)	1.03 (0.58, 1.84)
Cancer	44/ 73 (60.3)	0.97 (0.71, 1.34)
Circulatory disease	59/ 97 (60.8)	0.99 (0.75, 1.32)

Estimates are based on 1148 cohort members who were Queensland residents and had an onset date before 1 November 2020.

Table A11. Crude and age-sex-adjusted risks for inpatient hospital admission within two weeks of symptoms onset among Queensland residents with confirmed COVID-19 in relation to comorbid conditions, assuming patients with no QHAPDC records prior to onset had none of the measured comorbidities.

	Events/ persons (%)	Age-sex-adjusted RR (95%CI)
Asthma	<5/ 12 (<42)	1.15 (0.37, 3.63)
Chronic lower respiratory disease	5/ 13 (38.5)	1.48 (0.60, 3.66)
Diabetes	16/ 52 (30.8)	1.18 (0.69, 2.01)
Renal failure	5/ 19 (26.3)	1.00 (0.41, 2.46)
Cancer	20/ 73 (27.4)	1.07 (0.66, 1.74)
Circulatory disease	28/ 97 (28.9)	1.13 (0.74, 1.74)

Estimates are based on 1148 cohort members who were Queensland residents and had an onset date before 1 November 2020.

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CHAPTER 3

EVALUATION OF A SURVEILLANCE SYSTEM

The evaluation of Pen Computing System Population Aggregation Tool as a potential surveillance system for monitoring cardiovascular disease risk scores and appropriateness of treatment, for the Australian population

Table of Contents

List of Figures and Tables

Abstract

Background Cardiovascular disease (CVD) is the leading cause of mortality in Australia. Although CVD is largely preventable using lifestyle and pharmacotherapy measures, a significant proportion of the Australian population at high CVD risk are not receiving appropriate prevention therapy. A surveillance system for monitoring CVD risk and treatment would provide vital information on the magnitude, distribution and pharmacotherapy of CVD risk in the population. The Population Aggregation Tool Clinical Audit Tool (PAT CAT) produced by Pen Computing Systems (Pen CS), is widely available to PHNs across Australia, and has the capability to monitor CVD risk scores and treatment. This study aimed to: 1) evaluate whether PAT CAT could be used as a surveillance system for monitoring absolute CVD risk scores and appropriateness of treatment 2) provide recommendations for improvement and 3) initiate actions to enable improvements.

Methods The evaluation process was based upon the US Centers for Disease Control and Prevention guidelines for evaluating surveillance systems. This included assessment of system attributes and usefulness such as data quality assessment, stakeholder interviews, and the data usefulness. The evaluation was conducted using healthcare data from a single a general practice and PHN region, from June 2019 to June 2020.

Results PATCAT strengths are the data transfer from patient EHR to PAT CAT is accurate, it is possible to display population CVD risk scores, missing data, and proportions of people at high CVD risk not on appropriate medications. Weaknesses are a lack of a date range filter to only allow CVD risk scores to be calculated in those patients where all risk factors have been measured within a set time frame, and an inability to view CVD risk score and treatment trends over time. There were also interpretation issues with the

Heart Foundation CVD risk algorithm itself. For these reasons, PAT CAT is rarely used by relevant stakeholders.

Conclusion In its current format, PAT CAT is unable to act as a surveillance system for monitoring CVD risk scores and appropriateness of treatment. However, recommendations produced by this report regarding the necessary improvements for PAT CAT which will allow it to achieve surveillance status, are being implemented by Pen CS.

My role

This work was funded by a National Heart Foundation Vanguard grant. I wrote the grant for this in April 2018 and was awarded it in November 2018 (award ID 202253). Associate Professor Rosemary Korda and Dr Jason Agostino (my MAE supervisors) were co-investigators on this grant. The grant ($75,000) was used to appoint a project officer (Dr Victoria Coulton) to assist with data collection over 1 year. The project began in June 2019 and ended in June 2020. My role was in project design, supervision of data collection, all data analysis and the whole write up. This chapter has been prepared in a format suitable for publication which is the intention. I was involved in all meetings with stakeholders.

Lessons learnt

I improved my grant writing skills, learnt the value and importance of surveillance in chronic disease and noted the siloed approach to storage of health care data across the state and country. I also observed the ethical issues and complexities around data sharing between GPs, PHNs, hospital and registry data, differences between the Privacy Act 1988, and the Hospital and Health Boards Act 2011, that govern data use in each of

these two entities. I also learnt about the role of the PHNs and the influence of the Heart Foundation.

Public health impact

The information gained from this work has had some important impacts. Firstly, that our recommendations have been taken up by Pen CS and are being implemented which will allow the use of PAT CAT for PHNs and other stakeholders to monitor CVD risk and treatments (see letter from Pen CS in Figure 1A, Appendix). Secondly we are now able to look at linking CVD risk data and treatments across PHNs and states, using several approaches, one of which is using Primary Health Insights (PHI). PHI is a federally funded national data storage and analytics system designed to host the deidentified primary care data of Primary Health Networks (PHNs). Currently data from individual general practices are stored at the local PHN. PHI offers PHNs the opportunity to host healthcare data on the PHI platform. This means that data linkage across regions is possible. Discussions with PHI and Pen CS are underway to develop the necessary CVD risk score algorithms that will sit on the PHI platform to provide information on CVD risk scores and treatments across the population of Australia. This CVD algorithm will be used as a first demonstration of the ability of PHI concept.

The work from our report has been prepared for publication and will be submitted shortly. The results and knowledge gained from report have also formed part of an MRFF Cardiovascular Health grant in 2019 by Professor Emily Banks of which I was CI entitled: 'Predictive modelling to optimise cardiovascular disease risk assessment and management in Australia: how, when and who to screen' which only narrowly missed out on being successful. It also informed a successful NHMRC partnership grant (APP1169888) awarded in late 2019 entitled: 'Improving Communication about Heart

disease risk Assessment using Translational research strategies in General Practice (CHAT-GP): implementing guidelines through shared decision making' of which I am a CI. Further grant submissions are planned to fund the implementation of a national CVD risk score surveillance system including a NHRMRC partnership grant with the Heart Foundation.

I have also given several presentations on behalf of the Heart Foundation and local PHNs about this work to GPs and other stakeholders.

Acknowledgements

I would like to thank to Dr Victoria Coulton for all her hard work in collecting the data. Dr Zoltan Bourne GP for his extensive knowledge of CAT 4 and PAT CAT, plus access to his general practice. Natalie Haetzmann, Rob Major at Central Queensland, Wide Bay and Sunshine Coast PHN on their knowledge of PAT CAT at the PHN. Associate Professor Rosemary Korda and Dr Jason Agostino at the Research School of Population Health, Australian National University for help in design of the grant and project. Professor Tony Stanton, consultant cardiologist for his advice on project design. I would also like to thank the Heart Foundation of Australia for providing the funding.

Funding

This work was funded by a Heart Foundation of Australia Vanguard Grant (102253).

List of abbreviations

ACVDR: absolute cardiovascular disease risk

CAT4: Clinical Audit Tool

CDC: Centers for Disease Control and Prevention

CVD: cardiovascular disease

EHR: electronic health record

GP: general practitioner

HF: Heart Foundation of Australia

NHS: Nation Health Service

NVDPA: National Vascular Disease Prevention Alliance

PAT CAT: Practice Aggregation Tool For The Clinical Audit Tool

Pen CS: Pen Computer System

PHN: Primary Health Network

Background

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Australia, and its prevention is a National Health Priority (1-3). In 2016-17 CVD accounted for 11% of all hospital admissions within Australia and consumed 8.9% of the healthcare budget thus placing a significant health burden on the population (4). A large proportion of CVD is preventable primarily through targeting effective preventive medications and lifestyle interventions according to absolute CVD risk (5). A one-off, cross-sectional survey based on participants in the Australian Bureau of Statistics Health Survey of 2011-2012 found that 11% of the Australian population aged 45-74 years (approximately 811,000 people) without known prior CVD are at high absolute CVD risk meaning they have a >15% chance of a CVD event within 5 years (6, 7). High CVD risk individuals should be receiving both anti-hypertensive and lipid lowering medication, in addition to appropriate lifestyle advice (5). However, massive implementation shortfalls mean that 76% of these individuals are not receiving recommended preventive therapies (5).

The National Vascular Disease Prevention Alliance (NVDPA) of Australia guidelines recommend calculating an individual's CVD risk score using the absolute cardiovascular disease risk (ACVDR) calculator (5). This score is calculated by entering individual risk factors into a risk calculator based upon the Framingham risk equation. Combining risk factors provides a more accurate assessment of person's risk rather than using individual risk factors alone (8). The eight factors required to calculate the Australian ACVDR score are: age, gender, smoking status, systolic blood pressure, total cholesterol, HDL, diabetes, and presence of left ventricular hypertrophy (optional). A five-year risk score for the development of CVD is calculated and categorised according to whether a patient has low (<10%), moderate (10-15%) or high (>15%) CVD risk. The most recent 2012 risk score calculator treatment algorithm can be accessed directly at the Heart Foundation's

(HF) website and a version is usually embedded in the GP electronic health record (EHR) (9). Patients without prior CVD *and* who have a high ACVDR score, or moderate risk score with additional risk factors, are recommended to be prescribed both lipid *and* blood pressure-lowering therapy, and to receive lifestyle modification advice (5). Certain patients are automatically considered at high risk and do not need to have their risk calculated. For example, patients with prior CVD, or diabetic and over 60 years of age, or who have a cholesterol greater than 7.5 mmol/L. Patients in this group should be treated using the high risk treatment algorithm (5). Patients identified at moderate risk of CVD should be offered lifestyle modification advice and CVD risk review within 6-12 months. Patients identified at low risk of CVD should be offered lifestyle modification advice and CVD risk review in 2 years.

CVD preventive treatment is highly effective, with achievable reductions in blood pressure and lipids alone halving relative risk (8, 10). However, the effectiveness of preventive treatment depends on targeting treatment to individuals at the highest risk, which although recommended, is not being achieved in Australia. Furthermore, as there are no recent or ongoing estimates of CVD risk prevalence or appropriateness of treatments in Australia, ongoing implementation shortfalls will remain lethal. Improvements in detection, surveillance and management of risk would rapidly and readily translate into reductions in CVD disability, morbidity and mortality.

A surveillance system for monitoring CVD risk and treatment would provide vital information and understanding on the magnitude, distribution and pharmacotherapy of CVD risk in the population (11). It would also support evaluation of prevention strategies and facilitate planning for healthcare providers. If quality of care for CVD risk is to improve, such a system is needed to quantify assessment rates and appropriateness of treatment, and provide feedback to GPs and other healthcare providers. Currently, a

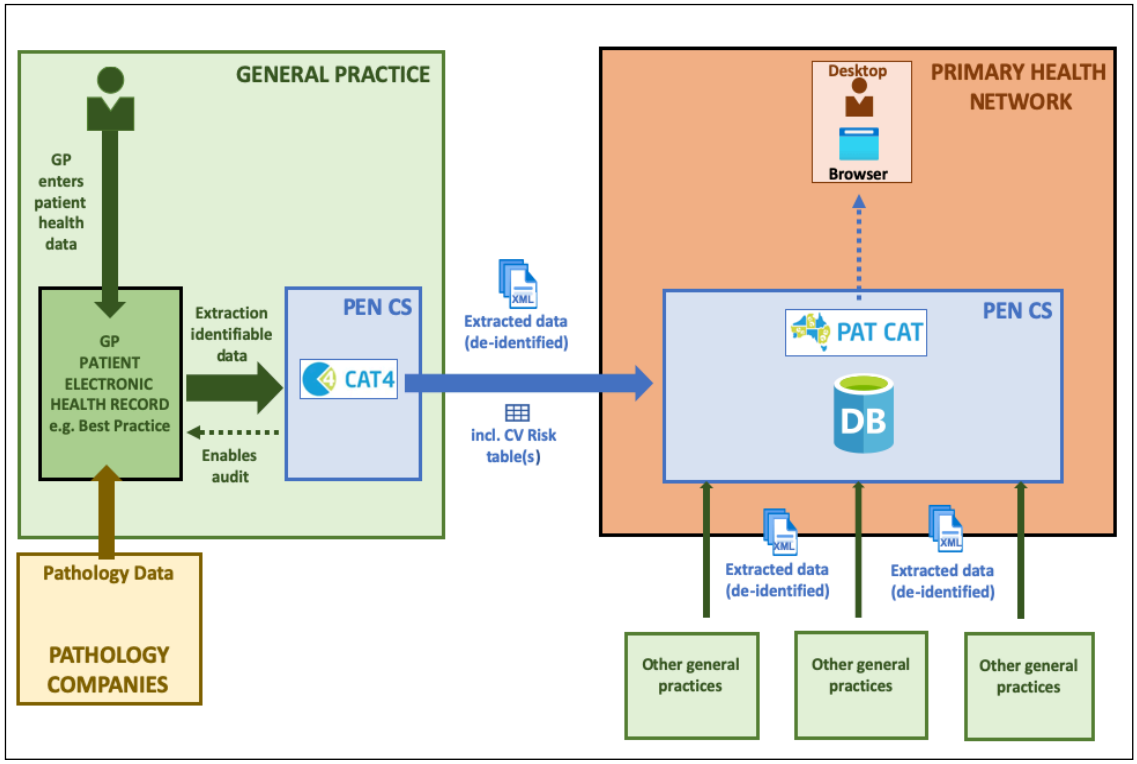
surveillance system for CVD risk and treatment does not exist in Australia and without one it will be more difficult to effectively achieve the public health goal of reducing CVD morbidity and mortality. Examples of the objectives of a CVD surveillance system are shown in Table 1. These include providing up-to-date information on the numbers and geographic regional location of patients eligible for CVD risk score assessment, numbers with and without risk scores available, the numbers of patients at high CVD risk who are not on appropriate therapy. Another important feature would be the ability use the information to feedback to PHNS and GPs on CVD assessment rates in theory region with goal of increasing risk score assessment rates and appropriateness of treatment.

Table 1. Objectives of a surveillance system for monitoring CVD risk and treatment

Objectives
Provide the total number of population available in the health analytics system used by that Primary Health Network
Provide the number of patients eligible for cardiovascular disease risk score assessment
Provide the number of patients with risk scores available
Provide the number of patients with no risk scores available
Provide the number of patients in each of the four risk score categories (Known high CVD risk, high CVD risk, moderate CVD risk, low CVD risk)
Provide the number of patients per risk factor missing
Provide the number of patients in each risk score category taking both anti-hypertensive and lipid-lowering therapies (dual therapy)
Provide the number of patients in each CVD risk score category taking either an anti-hypertensive agent OR a lipid-lowering therapy (monotherapy)
Provide the number of patients in each CVD risk score category on neither anti-hypertensive or lipid-lowering therapies (no therapy)
Provide the number of patients with Known high CVD risk, per cause
Provide the number of patients with no risk score available, on dual therapy
Provide the number of patients with no risk score available, on monotherapy
Provide the number of patients with pre-existing CVD
Provide the number of patients who have had a Heart Health Check
Provide the geographic regional location of data listed above

The technology for CVD surveillance lies latent within existing, widely distributed software in Australia. Pen Computer System (Pen CS) is a key provider of health analytics software for GPs and Primary Health Networks (PHNs) that enables population health analysis and reporting in the primary health care setting (12). 31 PHN organisations were set up in 2014-15 by the federal department of health in different regions across the country to improve the effectiveness of the delivery of medical services for patients (13). The role of a PHN is to coordinate the provision of health care by GPs, health services and other providers of health care. Pen CS covers 28 out of 31 PHNs across Australia (12) and currently serves 5,600 General Practices, 45,000 medical practitioners and 21 million patients (12, 14). One of Pen CS software tools used by GPs that is based within each practice is the *Clinical Audit Tool 4* (CAT4). This system allows GPs to undertake audits and health analyses on their own patient cohort data, including providing reports on patients' CVD risk scores and their treatments (Figure 1). The other tool used by PHNs is the *Practice Aggregation Tool For The Clinical Audit Tool* (PAT CAT) which monitors and surveys absolute CVD risk scores and treatments across populations. Because Pen CS has such a wide coverage, use of these systems could allow national CVD risk surveillance, which in turn could lead to improved healthcare delivery and CVD reduction in Australia. However, despite the potential abilities of CAT4 and PAT CAT to act as a surveillance system for monitoring absolute CVD risk and treatment, these systems have not been evaluated and are not widely used for this purpose.

Figure 1. Steps involved from entry of patient health care information including pathology data, into the general practice patient electronic health record, CAT4 (Clinical Audit Tool), PATCAT (Practice Aggregation Tool for the Clinical Audit Tool) and the Primary Health Network.



This study aimed to evaluate whether PAT CAT has the potential to be used as a surveillance system for monitoring across populations (1) absolute CVD risk scores, and (2) the proportions prescribed anti-hypertensive and lipid-lowering pharmacotherapy treatment according to their absolute CVD risk scores 3) make recommendations and 4) initiate action to make the necessary changes.

Methods

The evaluation process was based upon that outlined by the US Centers for Disease Control and Prevention (CDC) guidelines for evaluating surveillance systems (10), and then modified to fit the surveillance system under evaluation. The scope of the evaluation included system attributes which predominantly focussed on data quality, but also included simplicity, flexibility, acceptability, representativeness, timeliness,

stability. The evaluation also assessed system usefulness which referred to the value and practicality of the information generated by the surveillance system in relation to improving public health (see Table 2).

Table 2. Focussing the scope of the evaluation design: methods and measures used for evaluating attributes and usefulness risk scores and appropriateness of treatment of the Practice Aggregation Tool for the Clinical Audit Tool (PAT CAT) as a potential surveillance system for monitoring cardiovascular disease

Attribute	**Methods**	**Measures and questions used to assess the attribute**
Data quality	Data collection, audit, analysis	• Does the patient CVD risk data within CAT4 match with corresponding patient health records? • Does the PAT CAT aggregate CVD risk data match with individual patient health records? • Do the CAT4 and PAT CAT built-in calculators provide the correct risk score for patients?
Simplicity	Interviews	• How easy is CAT4 and PAT CAT to use? • How well is the information presented?
Flexibility	Interviews	• How responsive are Pen CS to requests for changes?
Acceptability	Interviews	• How often do staff and organisations to use CAT4 and PAT CAT?
Representativeness	Data analysis	• How representative is the data collected by PAT CAT?
Timeliness	Interviews	• How rapid are steps between the entering risk factors into the system and reporting the information?
Stability	Interviews	• How reliable is the system and how often are their outages?
Usefulness	PAT CAT assessment Interviews	• Can PAT CAT display the proportion of risk scores across the population? • Can PAT CAT display eligible patients with and without a risk score? • Can PAT CAT display patients who have incomplete sets of risk factors, and proportions missing in each risk factor category? • Can PAT CAT display the proportion of patients at high CVD risk not on guideline recommended therapy? • Can PAT CAT display trends over time? • How much is PAT CAT used by stakeholders?

CAT4: clinical audit tool; CVD: cardiovascular disease.

Setting

The setting was a single general practice and the local PHN based on the Sunshine Coast, Queensland, Australia. The practice used CAT4 and shared their data with their PHN for PAT CAT. The practice was situated in a small rural town (Modified Monash Model 5), 35 km from the nearest major hospital with a practice population of 3377 patients, 7 GPs, 6 nurses and 1 practice manager. The general practice was selected opportunistically, used Best Practice software as the EHR which is the one of the two majority EHRs used by general practices in Australia. The local PHN was the Central Queensland, Wide Bay and Sunshine Coast PHN which covers a population of 889,471 and 287 general practices (15).

Interviews

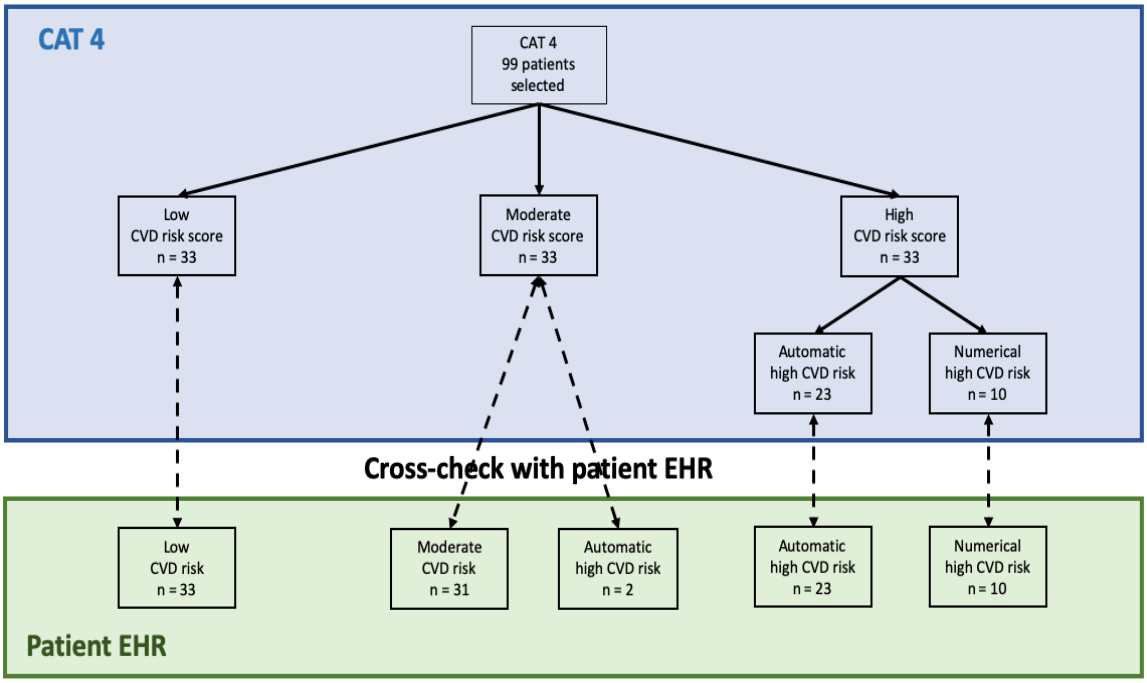
We engaged with major stakeholders who used Pen CS CAT4 and PAT CAT. These included members of the general practice (doctors, nurses and practice managers) and the local PHN (practice support nurses, senior managers and data analytics staff), as well as representatives from the Heart Foundation, Pen CS and the local hospital. The purpose of this was to gain understanding of the attributes of PAT CAT and CAT4 from the perspectives of the different of stakeholders. Face-to-face interviews were undertaken with staff at the general practice and hospital, and via teleconference with the Heart Foundation and Pen CS. In these interviews the format was informal but key topics were covered on how PATCAT and CAT4 functioned and the use of the system by staff. We then held a formal 4-hour meeting with all stakeholders together at the PHN. This had a formal agenda and covered the CDC listed topics regarding evaluation of a surveillance system. Written records of all meetings were kept.

Data quality

Access was provided to all patient EHRs held within the participating general practice at the time point for the month of June 2019. These were uploaded into CAT4, and from there to PAT CAT. As PAT CAT receives information directly from CAT4, it was necessary to check the accuracy of electronic data transfer across both of these platforms. The accuracy of the calculated risk scores within each system was also checked by entering individual patient values in the EHR into the HF 2012 CVD risk score calculator.

CAT4: To check the accuracy of transfer of data from the EHR into CAT4, 99 patients in total, (33 patients from each CVD risk score category, as determined by the CAT4 CVD risk calculator), were randomly selected from the CAT4 system of the participating general practice (Figure 2). At the patient level, the CVD health information from each individual was cross-checked back to the original patient health record data set.

Figure 2. CAT4 data quality assessment. Patients with different cardiovascular disease (CVD) risk scores were selected from CAT4 (Clinical Audit Tool) and validated by cross-checking with individual patient electronic health records (EHR).



PAT CAT: To check the accuracy of transfer of EHR data via CAT4 into PAT CAT, this initially required display of the number of patients eligible for CVD risk score assessment.

Using the filtration tool in PAT CAT, the number of patients in the practice population eligible for CVD risk score assessment was determined (supplementary material, Figure 1A). Those patients with no Indigenous status being recorded or did not have the all the necessary missing risk factors required for calculation, were excluded. Analysis was undertaken on those remaining eligible patients had sufficient CVD risk factors available to allow risk score to be calculated. To validate whether the PAT CAT data corresponded with that in the patient EHR, three test scenarios (A to C) were created and undertaken by applying different PAT CAT filter criteria to the eligible patients and the filtered results were cross-checked with the individual patient EHR. Each scenario was chosen on the basis of clinical relevance, involved a sufficient number of patients that was representative of accuracy, yet small enough to allow manual cross-checking of the individual patient EHRs.

Scenario A investigated the number of patients who were at high CVD risk and not on appropriate preventative pharmacotherapy. This required application of the following initial filter criteria: those patients aged 45 and over, non-indigenous, and an *absence of*: diabetes, hypertension, heart failure, cardiovascular disease (includes coronary heart disease, peripheral vascular disease, stroke, hyperlipidemia, familial hypercholesterolemia), ACE inhibitor/ARB, anti-thrombotics, beta blocker, calcium antagonist, diuretics, lipid modifying agents, oral hypoglycemics, injectable insulin. Following this, a further filter was applied to identify the number of patients at high CVD risk. Of the patients who met these filter criteria, we studied those identified as high CVD risk and reviewed the EHR of each these patients to confirm whether all of the above filter criteria were correct.

Scenario B focussed on those patients clinically at high risk due to diabetes and age over 60. The following filter criteria were applied to the patients eligible for CVD risk

assessment: age over 60 years, presence of diabetes and no prior CVD. Following this, a further filter was applied to identify the number of patients at high CVD risk. Those patients identified had their EHR records cross-checked for confirmation.

Scenario C focussed on patients at clinically determined high risk due to renal impairment not on appropriate preventative therapy. We applied the filter criteria of renal impairment and not on anti-hypertensive or lipid modifying drugs to the patients eligible for CVD risk assessment. Renal impairment must be actively coded by the GP in the EHR. Those patients identified, had their EHR records cross-checked for confirmation.

Ethics approval

Ethics approval for the study was provided by the Australian National University Human Research Ethics Committee (study protocol 2019/037).

Results

Description of CAT4 and PAT CAT systems

Figure 1 showed the flow of data from manual entry of patient health care information and pathology data, into the GP patient EHR. From there, data passes to CAT4 and then to PATCAT, whereupon PATCAT may be accessed remotely using a web browser. Examples of current EHRs that are compatible with CAT4 are Best Practice and Medical Director. For CAT4 and PAT CAT to calculate CVD risk, the GP is required to have recorded at least seven of the potential eight risk factors required, of which two - total cholesterol and HDL, are extracted automatically from the pathology lab results, if they are sent in the appropriate format.

CAT4 is used as a clinical audit tool within general practices. This enables GPs to perform analyses on their patient cohort data and allows reporting of key performance indicators back to their local PHN. This data is used to encourage improvements in health delivery at the individual practice level. For example, CAT4 automatically calculates a patient's ACVDR score provided the necessary data has been inputted into the GP EHR. CAT4 uses identifiable patient data which stays within the general practice. CAT4 produces reports that contain identifiable patient data that can be used by the GP, thus supporting clinical activities such as patient recall. Identifiable data never leaves the General Practice site unless consent is obtained.

General Practices using CAT4 can also participate and share their de-identified patient data with their PHN. Those general practices who participate can allow CAT4 software to export de-identified patient data to PAT CAT software which is hosted on designated servers at the PHN site. The uploaded health information on PAT CAT is accessible via a web browser in aggregate format to specified users. CAT4 sends a de-identified data set to PAT CAT at set time intervals. PAT CAT is able to provide aggregate CVD risk scores and also has inbuilt filter tools that allow further analyses, such as the type of treatments patients are receiving according to their risk score.

System Attributes

Data quality

CAT4

Of the 33 patients in the high risk group, CAT4 gave 10 patients a numerical absolute risk score value and the remaining 23 were recorded as 'automatic high risk'. Both those patients given numerical values and those considered automatic high risk, matched exactly with the online HF 2012 calculator (see supplementary material Table 1A). In the

moderate risk group, 31/33 patients risk scores agreed with the HF 2012 calculator as being at moderate risk (see supplementary material Table 1A). The two results that disagreed were categorised as 'automatic' high risk by the HF 2012 calculator. When referring back to the individual patient records, each of these patients had a total cholesterol of exactly 7.5mmol/L. Further investigation revealed that CAT4 calculator labels patients as automatic high risk if their total cholesterol level is ≥ 7.6mmol/l whereas the HF 2012 calculator considers ≥ 7.5mmol/L as automatic high risk. The NVDPA guidelines state that >7.5mmol/L (i.e. ≥ 7.6mmol/l) is automatic high risk and therefore the HF 2012 calculator is incorrect regarding the total cholesterol cut-point. In the low risk group, all CAT4 CVD risk score values agreed with the HF 2012 calculator. It is important to note that CAT4 did not include any patients with prior CVD.

Other quality issues noted were that although a CVD risk score is derived from those individual risk factors most recently available, these risk factors could be dispersed over a wide time period with sometimes years or decades between them. The clinical relevance of such a dispersed risk score is questionable. According the NVDPA guidelines, blood test values up to 5 years old, and 2 years old for blood pressure can be used (5). Another problem was that in many patients the blood pressure readings and cholesterol values were taken whilst patients were taking anti-hypertensive and/or lipid modifying medication and despite this, CAT4/PAT CAT provided a CVD risk score on these patients. The ACVD risk score was developed to be applied only to the treatment-naïve and, although it is possible to separate out those patients, the provision of a CVD risk score whilst on pharmacotherapy is of limited clinical value.

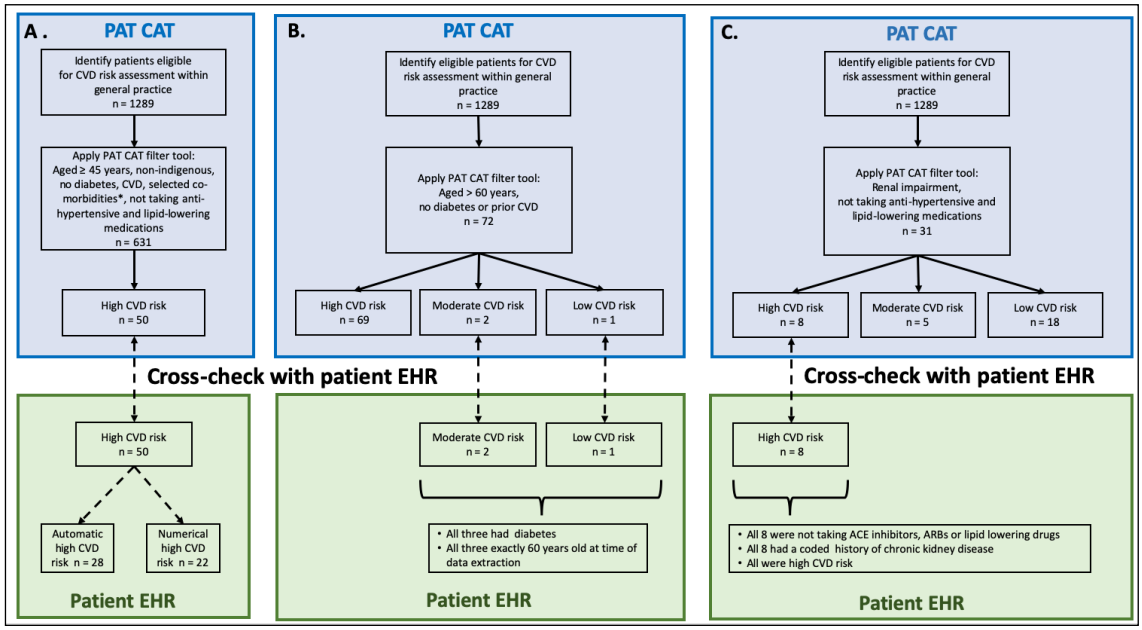
It also appeared that a patient's smoking status is incorrectly allocated. Patients should only be considered as being a 'non-smoker' once a 12-month period has elapsed following the date of smoking cessation. CAT4 incorrectly designates a patient a non-

smoker from the immediate point they stop smoking, and as a result, a patient's ACVD risk is underestimated.

PAT CAT

PAT CAT is able to display the number of eligible patients for CVD risk score assessment. Using the filtration tool in PAT CAT at the time of data extraction, the general practice had a population size of 3377 patients of whom 1741 were eligible for CVD risk score assessment (supplementary material, Figure 1A). Eighty-eight (5%) patients were excluded due to no Indigenous status being recorded and, for simplicity, we did not include the 22(1%) indigenous patients due to different age range for CVD risk assessment and small sample size. PAT CAT also identified that 342(20%) patients did not have the all the necessary missing risk factors required for calculation. This meant that 1289(75%) patients had sufficient CVD risk factors available to allow risk score to be calculated out of the original 1719 non-indigenous patients eligible. The three test scenarios were applied to these 1289 patients the results of which are shown in Figure 3.

Figure 3. PAT CAT (Practice Aggregation Tool for the Clinical Audit Tool) data quality assessment. Three scenarios A to C were created by applying different PAT CAT filter criteria to patients eligible for cardiovascular disease (CVD) risk score assessment. To check PAT CAT validity, those patients identified were cross-checked with the patient electronic health record (EHR).



*hypertension, heart failure, coronary heart disease, peripheral vascular disease, stroke, hyperlipidemia, familial hypercholesterolemia.

Scenario A (patients at high CVD risk and not on appropriate preventative pharmacotherapy). Six-hundred and thirty-one (49%) met the initial filter criteria, of whom 50(8%) were identified as high CVD risk. Review of the EHR of each these 50 patients confirmed all of the above criteria as being correct. Twenty-eight patients were automatic high risk, of whom 20 had a total cholesterol >7.5 mmol/L, five with a diastolic BP >110mmHg, 3 with a systolic BP >180mmHg. The remaining 22 had a numerical high CVD risk score with the same risk score values as the HF 2012 online calculator.

Scenario B (patients at high risk due to diabetes and age over 60). PAT CAT identified 72 patients with the initial filter, of whom it reported 69, 2 and 1 had a high, moderate and low CVD risk scores, respectively. According to national guidelines, all of these patients are at automatic high CVD risk. Review of the EHR of the moderate and low risk patients

confirmed that they were diabetic with no prior CVD, and exactly 60 years of age at the time of data extraction. We determined that their risk category depended upon how the risk score guidelines are interpreted. The HF 2012 calculator uses a cut point of ≥60 years to indicate automatic high risk whereas the written NVDPA CVD prevention guidelines uses a cut-point of ≥ 61 years (used by PAT CAT). This explains why these patients are not considered automatic high risk. Alteration of the PAT CAT filter criteria to include patients over 61 years old caused these 3 patients to disappear from the CAT4 report.

Scenario C (patients at high risk due to renal impairment not on appropriate preventative therapy). PAT CAT reported that 31 patients met the filter criteria and of these, 8, 5 and 18 patients were at high, moderate and low CV risk, respectively. Review of the EHR of the 8 high CVD risk patients, confirmed all had renal impairment, were not taking the listed medication, and were at high CVD risk. Six patients were automatic high risk due to a cholesterol level >7.5 (n=2), diastolic BP>110mmHg (n=1), or moderate or severe due to persistent proteinuria or a glomerular filtration rate of <45mL/min/1.73m2 (n=3), and two patients had a calculated CVD risk score of >15%. It is worth noting 'renal impairment' is a coded entry that must be selected by the GP who may not necessarily be using the same criteria as described by the NVDPA CVD risk guidelines (defined as persistently having a urine ACR > 25 mg/mmol for males or > 35 mg/mmol for females, or estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73m).

Simplicity

General practice staff reported that CAT4 was easy to use at the general practice level. At the PHN level staff report the user interface with PAT CAT is responsive, simple and intuitive with little training required. An extensive set of user instructions for PAT CAT

are also available on the Pen CS website (12). Staff noted that the filter enabling the automatic high risk patients to be filtered out for separate review available in CAT4 would be useful to have in PAT CAT. They also stated it would be helpful if PAT CAT could separate out and display automatic high risk patients into the causes of their high risk.

Flexibility

The staff at general practice reported the CAT4 system to be flexible but PAT CAT less so at the PHN level. Alterations to PAT CAT can be undertaken by Pen CS if required and can be carried out at predetermined time points during the year. From our project perspective, Pen CS have supported our evaluation of their software and promptly responded to any software enquires we had. They have agreed to review our findings and consider implementation of the recommendations. Indeed, some of our recommendations have already been implemented.

Acceptability

From a national perspective, acceptance rates by GPs and PHNs of CAT4 and PAT CAT are high - more than 80% of general practices use CAT4 and 28/31 PHNs in Australia are licensed to use PAT CAT. However, although considerable use is made by PHNs and GPs of CAT4, the actual use of PAT CAT for CVD risk score for analysis by PHNs is minimal, the reasons for which are evident from this study. Assessment rates by GPs of patients eligible for CVD risk assessment are known to be generally low. Although 80% of the patients in this practice population had sufficient risk factors to generate a risk score this does not mean that the patient had an actual CVD risk assessment undertaken. It merely indicates that sufficient risk factors have been measured at some point in the patient's past to generate a score. Staff pointed out that an electronic prompt system is

available. This is because those GPs who have used TOPBAR report there are software incompatibilities with their EHR leading to inadvertent slowing of the GP EHR especially during busy clinic times. Also, instalment of TOPBAR leads to multiple health alert notifications for other diseases during patient consultations which become a nuisance.

Sensitivity and predictive value

To calculate these for CAT 4 and PAT CAT, the true CVD risk scores of all the eligible patients in the practice would have to be known. From a practical perspective was not possible as it would have required the recall of all patients in the general practice for testing. CVD assessment rates of patients eligible for CVD risk assessment are known to be low nationally, and tackling this problem remains a major health issue (7). It was therefore our initial intention to estimate the sensitivity and positive predictive value by recalling a randomly selected, small group of low, moderate and high risk patients as identified by CAT4, and re-measure the ACVD risk scores in these patients. Due to the lock-down effects of the Coronavirus 2019 which was declared a global pandemic by the World Health Organisation on March 12th 2020, this part of the study could not be undertaken. We also determined that the other issues identified with CAT4 and PAT CAT in this evaluation study should be corrected first, in order to make such an undertaking worthwhile.

Representativeness

It is known that only a minority of those patients who are eligible for CVD risk assessment out of the general population have had their risk scores assessed and treated appropriately. One issue is that those who currently have CVD risk scores available in PAT CAT, will tend to be the sicker ones in the population, and therefore the

potential for selection bias exists. Furthermore, as these patients are more likely to receive treatment, PAT CAT data may suggest higher CVD risk scores and treatment levels than actually exist in the greater population.

PATCAT is widely available nationally with access to over 21 million patient records, and therefore from a coverage perspective, has the potential to provide the state of CVD risk scores and treatment across the majority of the Australian population. Currently however, aggregated data is confined to within single PHN area and cannot be shared across multiple PHN regions. This is because the data sharing agreements that currently exist between general practices and their respective PHNs only allow for aggregation of data within their PHN region, and do not allow for sharing with third parties or for the purposes of research. If full use of the data extracted from GPs is to be realised, then the data sharing agreements need to altered appropriately whilst protecting the rights of patients. Although PAT CAT generates risk scores, this does not indicate that a CVD risk assessment has taken place. PAT CAT does not record this currently and would require a means to record billing for a Heart Health Check by CAT4 and also to record when the inbuilt EHR CVD risk calculator has been used.

Indigenous Australians were not included in this study due to the small numbers provided by a single general practice. However, aggregation of this data at a national level would have important clinical and public health significance. Such data would complement information provided by two other data collections—the Online Services Report (OSR); and the national Key Performance Indicators (nKPI). These are funded by the Australian Government under its Indigenous Australians' Health Programme (IAHP) to deliver culturally appropriate primary health care services to Aboriginal and Torres Strait Islander people (28).

Timeliness

At the practice level through CAT4, a CVD risk score is available as soon as sufficient risk factors have been entered. It is currently the responsibility of the practice to review these scores and decide how to act upon the information that it provides. For most practices this is not occurring. Aggregate reports at a PHN level are available quarterly which is frequent enough to be representative of the CVD risk within the population. However, these are not being reviewed or made available to relevant stakeholders such as those working at the PHN, GPs, public health or health service staff or the Heart Foundation.

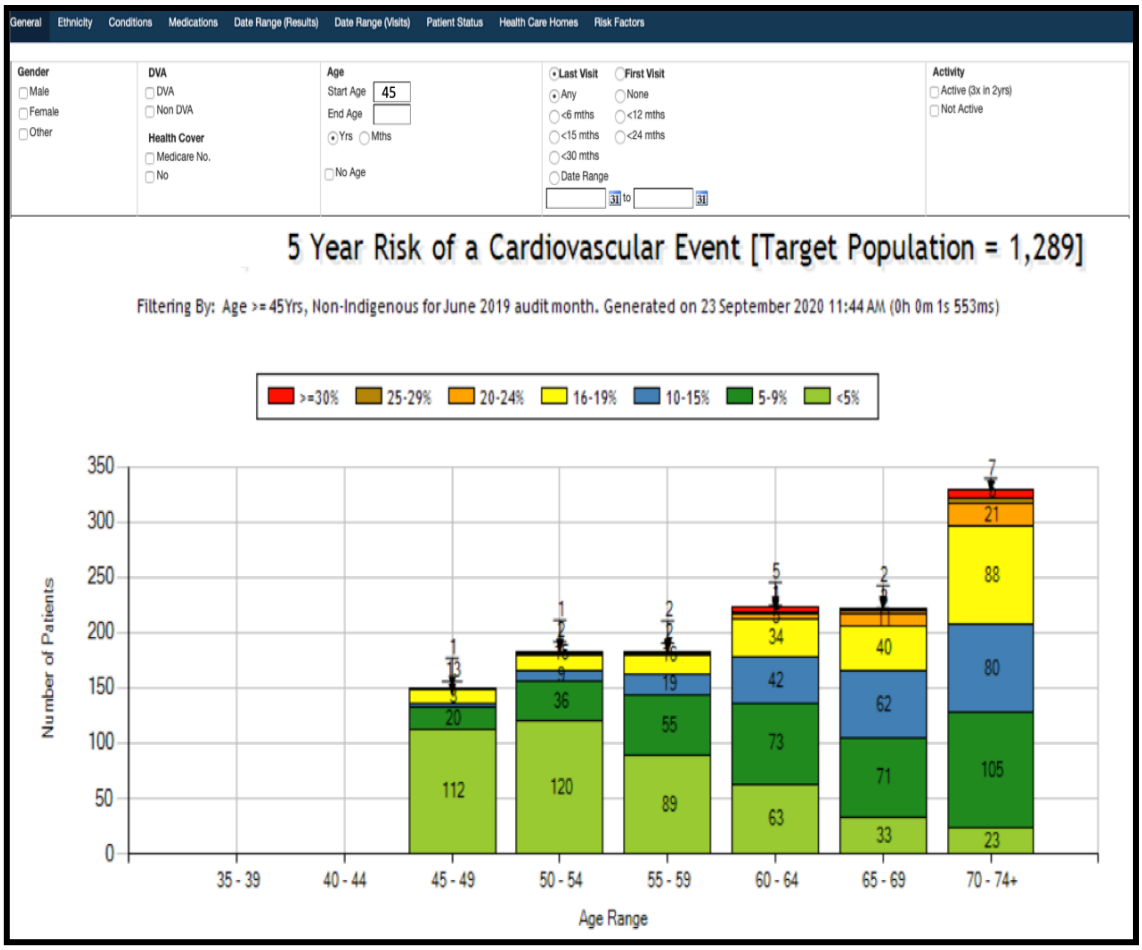
Stability

Interviews with GPs and PHN staff did not note any issues regarding unscheduled outages, prolonged down times or repair costs for Pen CS.

Usefulness

Using the PAT CAT inbuilt filter tools, we examined the capabilities of the PAT CAT system with regard to analysis of the uploaded CAT4 June 2019 aggregate data. In particular, the ability of PAT CAT to provide clinically useful reports on the extracted general practices aggregate data was assessed. Patients included for this assessment were as per the criteria for adults aged 45 and over without a known history of CVD. PAT CAT tool filters can be applied to show the numbers of patients with different risk scores according to age category (Figure 4). Although the numbers of patients in each risk category could be displayed, no date range filter tool is available to ensure all individual risk factors are measured within a set time frame. Risk scores are grouped at 5% increments, with seven risk groups in multiple colours, rather than in the three guideline-recommended <10%, 10-15% and >15% categories and easy-to-read traffic light colours.

Figure 4. Screen shot of the start page of the web browser for PATCAT, displaying some of the filter tool options used to view the numbers of eligible patients and their absolute cardiovascular disease risk scores across different age ranges, within a single general practice population.



A tabulated version is also available, and using additional filters, the proportions of patients in each risk score category can be displayed according to their different health characteristics (Table 3).

Table 3. Numbers and proportions of patients' cardiovascular disease risk scores according to their health characteristics in a single general practice, as determined by PATCAT.

	Proportion of total N(%)	N(%) in each CVD Risk Score category		
		Low	Moderate	High
Overall	1289(100)	800(62)	215(17)	274(21)
Female	696(54)	543(78)	49(7)	104(15)
Male	593(46)	255(43)	166(28)	172(29)
Smoker	155(12)	62(40)	36(23)	57(37)
Hypertension	378(29)	164(43)	72(19)	142(38)
Diabetes (type 1 or 2)	93(7)	11(12)	4(4)	78(84)
Taking anti-hypertensive medication	-	-	-	-
ACE inhibitors/ARB	299(23)	117(39)	51(17)	132(44)
Beta blockers	93(7)	33(36)	16(17)	44(47)
Calcium antagonists	90(7)	39(43)	18(20)	33(37)
Diuretics	137(11)	56(41)	26(19)	55(40)
Taking lipid-lowering medication	205(16)	80(39)	35(17)	90(44)

ACE: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CVD: cardiovascular disease; 'renal impairment' is a derived from a drop-down list of conditions in the patient electronic health record which must be actively selected by the GP

One valuable feature of PAT CAT is the ability to display the numbers of patients at high CVD risk not taking guideline recommended pharmacotherapy. In our report, 22% of patients with diabetes and over 60 years, were not taking guideline recommended pharmacotherapy (16). Out of 274 patients who identified to be at high CVD risk, 15% were not receiving anti-hypertensive medication, and 17% were not receiving lipid lowering therapy, and 13% were not receiving guideline-recommended dual therapy (Table 4). The greatest potential value of PAT CAT would be an ability to correctly display trends in levels of CVD risk scores and pharmacotherapy across populations. Currently

this is not possible. In contrast, CAT4 does have the capability to do this but this is at the general practice level. Other findings for PAT CAT were that although it was possible to display the numbers of patients on individual types of anti-hypertensive medications, it was not possible to show proportions of patients on anti-hypertensive medications as a group. This particular grouping filter is necessary to identify the numbers and trends of patients on appropriate medications. All of the filter results above could be downloaded in de-identified aggregate format as a CSV file.

Table 4. Numbers and proportions of patients with a high cardiovascular disease risk score not on anti-hypertensive or lipid lowering medications.

	Proportion of total N(%)	N(%) in each CVD Risk Score category		
		Low	**Moderate**	**High**
Diabetes > 60 yrs	72(77)	1(1)	2(3)	69(96)
Diabetes > 60 yrs, *not on anti-hypertensive OR lipid-lowering medications*	16(22)	1(6)	1(6)	14(88)
Familial Hypercholesterolemia	3(1)	0	0	3(100)
Familial Hypercholesterolemia *not on lipid-lowering medications*	1(33)	-	-	1(33)
Renal Impairment	80(6)	29(36)	20(25)	31(39)
Renal impairment *not on anti-hypertensive AND lipid-lowering medications*	31(39)	18(58)	5(16)	8(26)
Patients *not on anti-hypertensive medication*	928(72)	637 (69)	151(16)	140(15)
Patients *not on lipid lowering drug medication*	1084(84)	719(66)	181(17)	184(17)
Patients *not on anti-hypertensive AND a lipid lowering medication*	848(66)	614(72)	126(15)	108(13)

PAT CAT can also display those patients with missing values and including the numbers of patients and the types of missing CVD risk factor data (supplementary Table 2A). An HDL value was the most common single missing risk factor (29%), with 40% having both the total cholesterol and HDL values missing, and 22% had ≥3 risk factors missing. However, PAT CAT is not able to provide trends of information over time on those patients eligible for CVD risk assessment who do not have risk scores available, CVD risk scores or treatments.

In those patients where a CVD risk score has been obtained using parameters post-treatment, it would be useful to be able to determine CVD risk scores prior to drug therapy commencement. This would allow for the comparisons of pre- and post-therapy CVD risk scores. On review of individual health records, some patients had clinically appropriate reasons why preventative pharmacotherapy treatment had not been commenced. This information was often recorded as 'free text' information within the patient's medical notes. There is no specific field capability to denote this decision in the EHR and therefore Pen CS is unable to separate out this group.

It is important to note that although PAT CAT may provide a risk score, this does not mean that a risk assessment has been carried out by a GP. Assessment of risk by GPs are important as it indicates that the patient has had a specific consultation regarding their risk, and treatment decisions and lifestyle education has been discussed. Although not the direct aim of this study, we felt some means of recording whether of CVD assessment has been carried out by GPs was important.

Pen CS Software also has Topbar , a clinical decision support system embedded within practice clinical software to aid clinicians at the point of care. Topbar can provide automated notification to clinicians that certain patients are eligible for CVD risk assessment. However, Topbar software is not widely installed across all General

Practices even though it is free to GPs. It was also noted that no automatic notification system exists within Best Practice Software to alert the user that a patient has been identified as being at high ACVD risk by CAT4. Therefore, some patients identified as high risk by CAT4, may be going untreated.

Currently the CVD risk and treatment data provided by PAT CAT in its current format has limited value and explains why it is rarely used by the health system. The main issue is that CVD risk is being calculated from data collected over large date ranges, and a time filter capability is required. Access to PAT CAT is restricted to only members of the PHN which severely limits its use.

Discussion

This study evaluated PAT CAT to determine whether it can act as a surveillance system for monitoring absolute CVD risk scores, and the proportions prescribed anti-hypertensive and lipid-lowering pharmacotherapy treatment according to their risk scores, across the population. In its current format it is unable to do so. However, by assessing the individual attributes of surveillance systems as recommended by the guidelines of the CDC, we have identified areas for improvement and provided a list of recommendations (Table 5). If implemented, we believe that PAT CAT has the potential to act as a surveillance system for monitoring CVD risk and treatment across populations. To initiate this, these recommendations have been passed onto Pen CS who have agreed to make the changes. This report has also been passed onto all stakeholders and we are awaiting feedback.

The strengths of PAT CAT are that if sufficient risk factors are recorded in a general practitioner's EHR, these are automatically converted into correct CVD risk scores. PAT CAT is also able to accurately determine those patients at high CVD risk not on

appropriate preventative pharmacotherapy. In our report using a single general practice, 17% of high CVD risk patients are not on lipid lowering therapy, and 13% are not receiving dual therapy which is in keeping with published data (7). Another major strength is the national coverage of Pen CS, with 90% of PHNs licensed to use the product and 80% of the Australian population on the system, meaning true population surveillance is possible (12). The main weaknesses of PAT CAT are a lack of a date range filter and inability to share aggregate data between PHNs. Although all the individual risk factors may be present, they may have been collected over a wide date range and therefore no longer clinically relevant. Insertion of a simple date range filter would allow determination of the overall risk in a population within a recent time frame.

It is also important that the information held by PAT CAT be made accessible to relevant stakeholders. Currently, only members of the PHN have access as current data sharing agreements do not allow access for external groups such as the Heart Foundation or health policy makers. In order for this to occur, the GP-PHN data sharing agreements will need to be altered. A new national federally-funded initiative called Primary Health Insights may overcome this by providing a platform for PHNs to store their data and allowing aggregation of data across states. PHI relies predominantly on the data sets provided by Pen CS. We would also suggest that the data sharing agreements be altered to allow for the de-identified data to also be made accessible for research.

Our study has also detected errors in the official HF 2012 calculator itself which may have arisen due to ambiguities in the guidelines themselves. We also noted there is a significant issue with the EHR inbuilt CVD risk calculator (Best Practice) which appears to be using an out of date version, resulting in almost 60% of all high risk patients being recategorized to a lower risk group or not all (see supplementary material, Table 1A and

text). As Best Practice EHR is used by over half of all general practices in Australia, many patients are at risk of not receiving appropriate CVD prevention therapies (17).

In Australia, despite national guidelines recommending all eligible patients 45-74 years be screened, only half of those eligible have essential CVD risk factors recorded, and use of the CVD risk calculator is even lower at 17%. One survey of over 100 Australian GPs found that 30% of GPs self-reported screening less than 60% of their eligible patients, and one in ten not screening at all (18). Unfortunately, low assessment rates are likely to translate into low treatment rates which can lead to an excess of cardiovascular events. This was shown in a study examining the absolute CVD risk scores in patients presenting to hospital with acute coronary syndrome, and the proportions on guideline-recommended pharmacotherapy according to their score (19). Two-thirds of all patients presenting had no prior history of CVD, of whom 36% were established to have a high CVD risk score prior to their ACS presentation. Of these, 80% were on incomplete or no guideline-recommended pharmacotherapy.

A CVD surveillance system would support improvements to quality of care for CVD risk by quantifying the numbers of patients at risk, their assessment rates and appropriateness of treatment. These results need to be then fed back to GPs and other healthcare providers to encourage change in practice (20). Such a system — lacking in Australia — would also support data collection necessary for local CVD risk equations, evaluation of prevention strategies and healthcare planning.

It is also worth mentioning that there are 3 other health analytics providers in use by GPs and PHNs that also extract deidentified data: POLAR owned by Outcome Health, Primary Sense owned by Gold Coast Primary Health Network, and MedicineInsight which is part of NPS MedicineWise and funded by the Australian Department of Health

(25-27). If the CVD data extracted by these systems are to be included, the same evaluation process of their surveillance systems would also have to be undertaken.

The use of data from EHRs has enabled epidemiologists to conduct cross-sectional and longitudinal investigations of CVD risk without the burdens imposed by assembling traditional cohort studies. EHR data can be leveraged as an existing data source to conduct rapid and more efficient investigations into the population burden of CVD and its risk factors (21). To our knowledge, whilst aspirational, globally there are no EHR systems in current use that undertake surveillance of CVD risk at population level. However, in England this may soon change. All GP practices in the UK are owned by the National Health Service (NHS) and therefore have the same EHR. NHS England are soon to be implementing CVDPREVENT, a national primary care audit that will automatically extract routinely held GP data covering diagnosis and management of six high risk conditions that cause stroke, heart attack and dementia: atrial fibrillation (AF), high blood pressure, high cholesterol, diabetes, non-diabetic hyperglycaemia and chronic kidney disease (22). The potential benefits of what a large surveillance system for CVD risk can provide are highlighted by the New Zealand Predict Cardiovascular Disease Cohort (23). In New Zealand, there is widespread use of EHRs by general practices and the PREDICT decision support system has been inserted into 40% of general practices EHRs. As a result, there have been improvements in documentation and classification of risk, risk factors and medical history in general practice. When PREDICT software was first introduced in 2012, CVD risk assessments were at 3% of the total cohort and have since risen to 79-88% by 2015 (23). First and recurrent ischemic heart disease events in New Zealand are also in decline (24).

Strengths and limitations

This study undertook an in-depth investigation of Pen CS CAT and PAT CAT matching CVD risk scores with individual patient notes following the CDC guidelines. The limitation of this study was that this was carried out in a single GP practice, but it is unlikely that the electronic transfer of data is dissimilar in other practices. The general practice involved used Best Practice EHR and ideally, we would have included practices that used other EHRs such as Medical Director. More extensive scenarios involving greater numbers of patients when checking the validity of PAT CAT back to the EHR would have been useful, but would have been beyond the resources available for this study. We have also assumed that general practice staff are obtaining the risk factors for CVD assessment in a standardised manner. Should the recommendations be implemented, then the next step would be to test whether the linked aggregate data was representative of the CVD risk in the target (national) population.

Conclusion

This study has shown that in its current format PAT CAT is unable to act as a surveillance system for either cardiovascular disease risk score monitoring in the population, or the appropriateness of preventative pharmacotherapy. However, PAT CAT does have significant potential and we have provided a list of recommendations that, if implemented, will allow to achievement of these goals. We also discovered errors with both the HF 2012 calculator and NVDPA guidelines which are causing patients to be incorrectly risk categorised and may be adversely affecting patient outcomes.

Table 5. List of recommended changes required to improve PAT CAT.

Recommendation	Reason	Level of Need	Responsibility
PATCAT: a date range filter tool to allow for the CVD risk scores to be calculated only in those patients where all the risk factors had been measured within a set time frame. Ideally this time frame could be altered (from anywhere between 3 months to two years)	This overcomes the issue that a patient's risk factors may have been collected over a wide time range – decades sometimes, and are therefore not relevant	Essential	PenCS
PATCAT: capability to choose to display a risk score in patients taking, or not taking anti-hypertensive + lipid lowering medication	CAT4 risk scores are calculated whilst patients are on medication. The ACVD risk score was developed to be used only on patients who are treatment naïve.	Essential	PenCS
CAT4: patients can only be considered as being a non-smoker once a 12-month period has elapsed following the date of smoking cessation *may need a date to be entered recording when stopped	CAT4 wrongly designates a patient a non-smoker from the immediate point they stop smoking.	Essential	PenCS
PATCAT: ability to provide results over different time points (snapshots)	Review trends	Desirable	PenCS
PATCAT: Graphical CVD risk displayed as per the NVDPA guidelines in three groups using their percentage ranges and colour system (low <10%, moderate 10-15%, high risk >15%).	PATCAT currently displays aggregated patient CVD risk scores across seven risk groups and in different colours	Essential	PenCS
PATCAT: provide an additional category: 'no risk score' available	This would help display trend over time of eligible patients being assessed.	Essential	PenCS
PATCAT: A filter within PATCAT to enable the automatic high-risk patients to be displayed separately. This is possible in CAT4 but not in PATCAT.	Compare proportions at automatic high-risk vs other risk groups	Desirable	PenCS
PATCAT: A tool within PATCAT to enable the automatic high-risk patients to have the *cause* of their high-risk category displayed	Provide understanding of causes of automatic high risk	Desirable	PenCS

Recommendation	Reason	Level of Need	Responsibility
PATCAT: Ability to divide and display patients into 'no prior CVD' and 'prior CVD'	Prior CVD receives different treatment	Essential	PenCS
PATCAT: update the legend beneath graph of 5-year Risk of Cardiovascular Event so it states it is using the 2012 NVDPA calculator.	Current legend states it is using the NVDPA absolute CVD risk calculator from 2009 which is incorrect.	Essential	PenCS
PATCAT: Ability to display the total number of patients with no prior CVD, eligible for CVD risk assessment	This number divided by the number of patients who have been screened provides the proportion of patients screened.	Essential	PenCS
PATCAT: Ability to display numbers/proportions of patients who have complete/incomplete sets of risk factors available for risk score calculation. Includes ability to display numbers/ proportions missing in each risk factor category	Ability to monitor progress of numbers/ proportions of patients who have RF available/missing, and which risk factors are not being measured.	Essential	PenCS
PATCAT: Ability to display numbers of patients who have incomplete set risk factors, and proportions missing in each category.	Ability to determine which risk factors are not being measured	Essential	PenCS
PATCAT: Ability to display numbers of patients taking any anti-hypertensive agent as a group	Ability to determine how many patients are taking any anti-hypertensive agent as a group	Desirable	PenCS
PATCAT: Ability to display numbers of patients in each risk score category, on both anti-hypertensive and lipid lowering therapy, single therapy, or no therapy	Ability to determine its appropriateness in relation to risk category.	Essential	PenCS
PATCAT: Ability to display number/proportion of patients within a certain risk score category pre-treatment, then their most recent risk score post-treatment	Ability to see change in risk score following drug/lifestyle therapy commencement.	Desirable	PenCS

Recommendation	Reason	Level of Need	Responsibility
PATCAT: Ability to display number/proportions of patients that have had/not had a CVD risk score assessment *within certain specified date ranges*	Ability to monitor CVD risk up-to-date risk assessments. This would require CAT4 (and PATCAT) to be able to detect when the PMS inbuilt CVD risk calculator has been used for a patient.	Essential	PenCS
PATCAT: Ability to display numbers of patients that have had a Heart Health Check.	Ability to monitor CVD risk assessments.	Essential	PenCS
TOPBAR: Ability to display notification to clinicians that certain patients are eligible for CVD risk assessment	Ability to help GPs increase their assessment rates	Desirable	PenCS
PATCAT: hypertension should not be included as a 'Cardiovascular Disease'	Ensure 'Cardiovascular Disease' has correct components	Essential	PenCS
Update data sharing agreements to allow data aggregation across PHNs at state and/or national level.	Ability to allow CVD risk score surveillance and appropriateness of treatment across state and/or nation	Essential	PHNs, Heart Foundation, GPs
Heart Foundation to address disagreement between NVDPA CVD risk guidelines and the HF calculator regarding the total cholesterol cut-point	NVDPA guidelines state >7.5mmol/L is automatically at high risk. The HF 2012 calculator considers ≥ 7.5mmol/L automatic high risk.	Essential	Heart Foundation
Heart Foundation to address disagreement between NVDPA CVD risk guidelines and the HF calculator regarding the >60 years cut-point for diabetes and automatic high risk.	HF 2012 calculator uses a cut point of ≥ 60 years. The NVDPA guidelines state that the presence of diabetes and >60 years. CAT4/PATCAT uses ≥ 61 years.	Essential	Heart Foundation
PenCS to update their website so that it states they use the Heart Foundation 2012 calculator	The website with the bar column representation of aggregate risk scores currently states in the bottom legend they are using the Heart Foundation 2009 calculator	Essential	PenCS

Recommendation	Reason	Level of Need	Responsibility
Regular review of NVDPA guidelines by PenCS, Best Practice and other general practice PMS providers.	Ensure the CAT4 and PAT CAT remain up-to-date and can make necessary changes. (new guidelines are due, web-based calculator may be recommended)	Essential	PenCS
For new future ACVD risk guidelines, check that those issued are clear and non-ambiguous, and in complete agreement with the risk calculation algorithm.	This will avoid misunderstanding, ambiguities and errors.	Essential	NVDPA and Heart Foundation
Make access to PATCAT available to other relevant stakeholders, including for research,	Ensure stakeholders., including researchers, have access to relevant information which will better inform those monitoring, making implementation measures.	Desirable	PHN, GPs, Heart Foundation.

Supplementary material

Figure 1A. Flow diagram of selection of patients eligible for cardiovascular disease (CVD) risk assessment

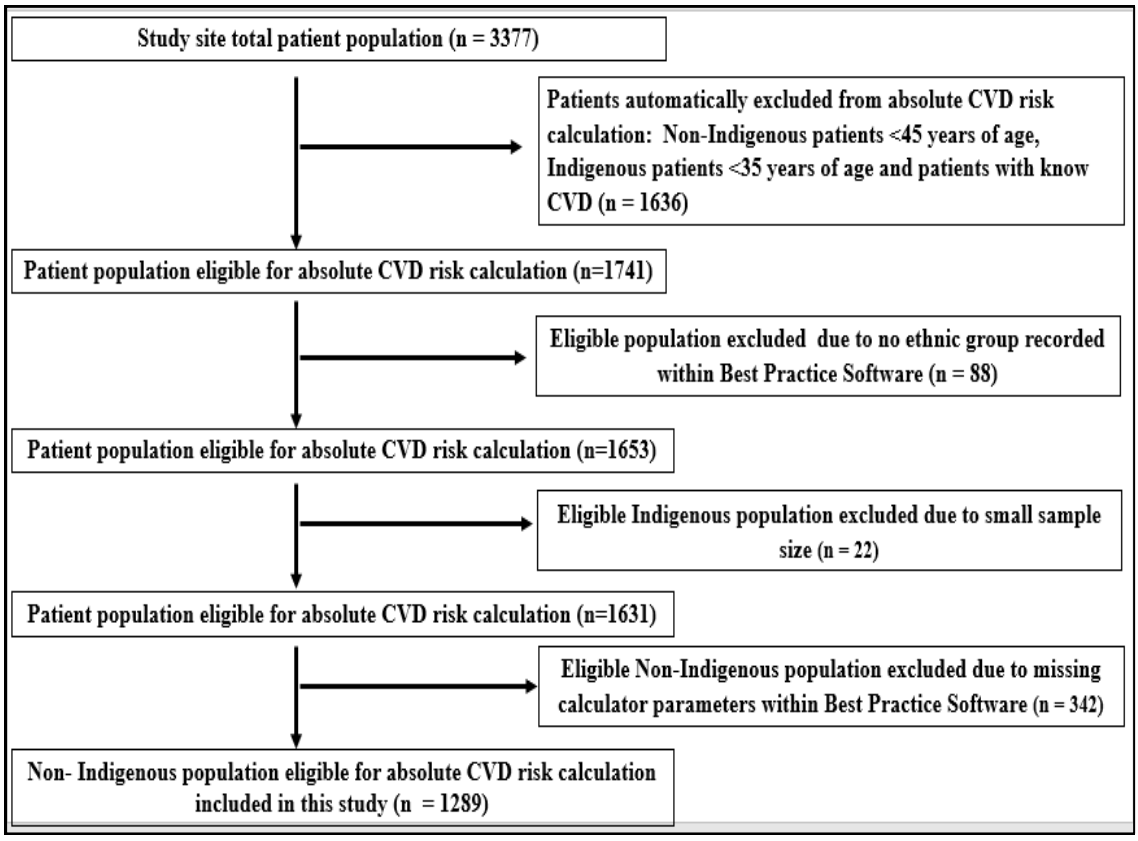


Table 1A. Comparison of absolute cardiovascular disease risk scores for individual patients using the CAT4 and the Heart Foundation 2012 risk calculator. Also included are risk scores derived using the in-built electronic health record calculator (Best Practice) and the Heart Foundation 2009 risk calculator. See text below for description of results.

Risk Category	Patient (age stated if >74 yrs)		CAT4 calculator	Heart Foundation 2012 calculator	Best Practice calculator	Heart Foundation 2009 calculator
High CVD Risk	>74 years	1 (77)	24%	24%	27%	27.4%
		2 (79)	16%	16%	18%	18.6%
		3(83)	20%	20%	25%	25%
		4(76)	23%	23%	24%	24%
	<74 years	5	19%	19%	19%	19.5%
		6	19%	19%	19%	19.8%
		7	19%	19%	18%	18.6%
		8	16%	16%	15%	15.6%
		9	16%	16%	15%	15.9%
		10	31%	31%	31%	31.0%
Moderate CVD Risk	>74 years	1 (78)	13%	13%	14%	14.4%
	<74 yrs.	2	10%	10%	9%	9.9%
		3	13%	13%	12%	12.5%
		4	11%	11%	11%	10.5%
		5	12%	12%	12%	12.4%
		6	12%	12%	11%	12.0%
		7	10%	10%	10%	10.0%
		8	12%	12%	11%	11.9%
		9	13%	13%	13%	13.4%
		10	11%	11%	10%	10.6%
		11	13%	Automatic High Risk	12%	12.9%
		12	14%	14%	14%	14.3%
		13	11%	11%	10%	10.7%
		14	13%	13%	12%	13%
		15	12%	12%	12%	12.2%
		16	11%	11%	10%	10.6%
		17	10%	10%	9%	9.9%
		18	14%	14%	14%	14%
		19	14%	14%	14%	14.2%
		20	13%	13%	12%	12.8%
		21	13%	13%	13%	13.2%
		22	11%	11%	11%	11%
		23	10%	10%	10%	10.1%
		24	13%	Automatic High Risk	13%	13.2%
		25	12%	12%	12%	12.4%
		26	14%	14%	13%	13.7%
		27	13%	13%	13%	13.2%

		28	10%	10%	10%	10.1%
		29	10%	10%	10%	10.1%
		30	14%	14%	13%	13.9%
		31	10%	10%	10%	10.3%
		32	11%	11%	11%	11.3%
		33	11%	11%	11%	11.3%
	>74 years	1 (81)	8%	8%	10%	10.3%
		2 (90)	4%	4%	7%	7.6%
		3 (76)	4%	4%	4%	4.5%
		4 (87)	7%	7%	10%	10.8%
	<74 yrs.	5	2%	2%	1%	1.8%
		6	3%	3%	2%	2.8%
		7	2%	2%	2%	2.1%
		8	4%	4%	4%	3.7%
		9	6%	6%	6%	6.1%
		10	7%	7%	6%	6.8%
		11	7%	7%	6%	6.7%
		12	6%	6%	6%	6.3%
		13	9%	9%	9%	9.2%
		14	2%	2%	2%	2.1%
		15	2%	2%	1%	1.9%
		16	8%	8%	7%	7.8%
		17	2%	2%	2%	2.4%
Low CVD Risk		18	2%	2%	2%	2.1%
		19	2%	2%	2%	2.3%
		20	6%	6%	5%	5.8%
		21	4%	4%	3%	3.7%
		22	7%	7%	7%	7.1%
		23	4%	4%	3%	4%
		24	7%	7%	6%	6.9%
		25	8%	8%	8%	8.1%
		26	6%	6%	6%	6.8%
		27	5%	5%	4%	4.6%
		28	7%	7%	6%	7.0%
		29	4%	4%	3%	3.7%
		30	6%	6%	6%	6.3%
		31	3%	3%	3%	3.2%
		32	0%	0%	0%	0.5%
		33	0%	0%	0%	0.5%

CVD: cardiovascular disease

Supplementary text: Checking the Best Practice EHR inbuilt CVD risk calculator validity.

In the four patients over 74 years of age, the Best Practice (BP) EHR calculator overestimated CVD risk when compared to the HF 2012 calculator. The reason is that the HF 2012 calculator only allows a maximum age of 74 to be entered and ages above this are given a value of 74. This similar to the HF 2009 calculator in which values over the age of 74 can be entered, and the greater the value entered, the greater the proportional risk. We suspect BP is still using the HF 2009 calculator. For the six patients under 74 years old both calculators had very similar results. The only difference was that the BP EHR calculator appears to incorrectly round downwards giving a 1% lower value. Importantly, no patients were re-categorised. In the 23 patients verified to be at automatic high risk, BP EHR calculator lacked the ability to categorise them, presumably because this feature was only introduced in the 2012 ACVD risk guidelines. Therefore, the BP EHR calculator gave these patients absolute risk scores values. Four (17%) were identified as high risk, 48%(11) moderate risk, 26%(6) low risk, and in 9%(2), no risk was able to be determined as these patients had missing data parameters. Overall, out of all the high risk patients, the BP EHR calculator incorrectly categorized 58%(19) patients to a lower risk group or not at all. In the moderate and low risk groups, two patients (6%) from each group in each were recategorized by BEHR calculator to be low and moderate risk, respectively. In these groups, the BP EHR derived values were very similar to the HR 2009 calculator.

Table 2A. Practice Aggregation Tool for the Clinical Audit Tool (PAT CAT) display of the missing values with regard to the numbers of patients and the types of cardiovascular risk factor data in a single general practice population.

Missing Patient Data Parameters	**Patient Numbers**
Total Cholesterol and HDL values missing	40% (n = 138)
HDL value only missing	29% (n = 99)
3 or more data parameters missing	22% (n = 74)
Blood pressure value only missing	4% (n = 14)
Smoking only missing	2% (n = 7)
Smoking status and HDL value missing	1% (n = 4)
HDL value and blood pressure reading missing	1% (n = 4)
Smoking status and blood pressure reading missing	1% (n = 2)
Smoking status and HDL value missing	0
Total cholesterol and blood pressure reading missing	0
Total cholesterol value only missing	0
Total number of eligible Non-Indigenous patients excluded	342

HDL: high density lipoprotein

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CHAPTER 4

EPIDEMIOLOGICAL PROJECT

A cross-sectional survey describing general practitioners' absolute cardiovascular disease risk assessment practices and their relationship to knowledge, attitudes and beliefs about cardiovascular disease risk in Queensland, Australia

Published in *BMJ Open* August 2020; volume 10, issue 8.

http://dx.doi.org/10.1136/bmjopen-2019-033859

Table of Contents

Abstract

Objectives To describe general practitioners' (GPs) absolute cardiovascular disease risk (ACVDR) self-reported assessment practices and their relationship to knowledge, attitudes and beliefs about ACVDR.

Design Cross-sectional survey with opportunistic sampling (October to December 2017)

Setting Sunshine Coast region, Queensland, Australia.

Participants 111 GPs responded to the survey

Primary and secondary outcome measures Proportion of GPs reporting a high (≥80%) vs moderate (60-79%)/low (<60%) percentage of eligible patients receiving ACVDR assessment; proportion agreeing with statements pertaining to knowledge, attitudes and beliefs about ACVDR and associations between these factors.

Results Of the 111 respondents, 78% reported using the Australian ACVDR calculator; 45% reported high, 25% moderate and 30% low ACVDR assessment rates; >85% reported knowing how to use ACVDR assessment tools, believed assessment valuable, and were comfortable with providing guideline-recommended treatment. Around half believed patients understood the concept of high risk and were willing to adopt recommendations. High assessment rates (vs moderate/low) were less likely among older GPs (≥45 vs ≤34 years, age-sex-adjusted OR [aOR] 0.36, 95%CI 0.12-0.97). Those who answered knowledge-based questions about the guidelines incorrectly had lower assessment rates, including those who answered questions on patient eligibility (aOR 0.13, 0.02-1.11). A high assessment rate was more likely among GPs who believed there was sufficient time to do the assessment (aOR 3.79, 1.23-11.61) and that their patients were willing to undertake lifestyle modification (aOR 2.29, 1.02-5.15). Over 75% of GPs agreed better patient education, nurse-led assessment and computer-reminder prompts would enable higher assessment rates.

Conclusions Although the majority of GPs report using the ACVDR calculator when undertaking a CVD risk assessment, there is a need to increase the actual proportion of eligible patients undergoing ACVDR assessment. This may be achieved by improving GP assessment practices such as GP and patient knowledge of CVD risk, providing sufficient time and nurse-led assessment.

My role

I was the lead researcher in this study. I conceptualised the idea and was responsible for designing the protocol, survey questionnaires, ethics and research governance submissions.

I was actively involved in carrying out the study. I organised and presented at meetings with GPs in our region to inform them about the study. I supervised and participated in the distribution of the surveys to GPs directly and also collection of the completed surveys. I was responsible for all of the data analysis, manuscript writing and submission. I organised and received assistance from medical students and junior doctors in the distribution and collection of the surveys (paper and digital). They are listed as co-authors. The data entry was undertaken by a research assistant, overseen by myself to monitor quality. The work also involved collaboration with members of the National Centre for Epidemiology and Population School of Health (RK and JA) and also a cardiology colleague Professor Tony Stanton. They provided advice on study design and analysis and interpretation of data, and they reviewed the manuscript critically for important intellectual content.

In addition to publication of the study findings, I was responsible for their dissemination at several conferences, meetings and webinars. These included the:

- National Primary Health Network Conference, Sydney 2019

- Presentation for the Heart Foundation to GPs as a national webinar, Sydney, April 2019
- Brisbane Primary Health Network and on behalf of the Heart Foundation, to GPs and other allied health practitioners, Brisbane March 2019.
- To the local community, as part of a CVD prevention drive on the Sunshine Coast Queensland, March 2019 and February 2021.

This work led to additional related research within the period of my degree: 'Absolute cardiovascular disease risk score and pharmacotherapy at the time of admission in patients presenting with acute coronary syndrome due to coronary artery disease in a single Australian tertiary centre: a cross-sectional study', also published in *BMJ Open* in 2021 (1). This work showed that a large proportion of patients presenting to hospital with acute coronary syndromes due to coronary artery disease were at high risk of developing CVD prior to the event and most were not on guideline-recommended treatment. This evidence further reinforces a greater need for more CVD risk score assessments and treatments.

Lessons learnt

I learnt about the importance of prevention of cardiovascular disease and its role in public health, as well as the value of surveys and qualitative research. I come from a background in cardiovascular physiological interventional research which, up until recently, involved giving drugs and observing physiological responses on human volunteers both with and without disease. Therefore, this was quite a change for me, in terms of methods and the field of research (i.e. prevention). On reviewing the literature on cardiovascular disease prevention, I noted the low levels of measuring of CVD risk scores and low rates of treatments. However, on speaking with GPs, they

believed they were assessing CVD risk and treating appropriately. Representatives of the Heart Foundation and Primary Health Networks reported that they were being met with the similar responses when encouraging GPs to undertake more risk score assessments. Both GPs, PHNs and Heart Foundation asked for local evidence that risk score assessments were not being performed. Therefore, we undertook this simple survey to help show that risk assessments were occurring at a low level and was found to be very valuable to those promoting CVD prevention to GPs. It has also been useful in validating me as someone who has undertaken credible research in this area.

I also gained experience in the use of online surveys. The study was intended to be a survey of local GPs. However, the online version of the survey got passed onto an online website called 'Doctors Down Under' by a particularly enthusiastic GP. This meant that GPs from other states also answered the questionnaire. Unfortunately, we were unable to include these results due to our ethics permission being only valid within our state. We explored the possibility of an amendment but hospital-related ethics committees (in our case the Royal Brisbane and Women's Hospital Research Ethics Committee) are only able to give permission for locally run health service research and not research in other states. As we were time limited, resource poor and the numbers of extra GPs that could be included were relatively small, I decided that the extra effort was not worthwhile. This highlighted to me the limitations of local hospital ethics permission and the potential advantages of a national ethics committee.

Public health impact

The peer-reviewed research has been published in *BMJ Open* (see manuscript later). I have presented the findings at national conferences, a Heart Foundation organised national webinar to GPs, and also at several local events to both GPs and community

events promoting CVD prevention. As a result, this and other work related to this thesis (see earlier), I was asked to attend a workshop to assist in the development of new national guidelines on CVD Prevention for Australia. The Heart Foundation policy makers have also used my publications as evidence for GPs that CVD risk assessment rates are low. It has also led to me working closely with the Heart Foundation providing advice on CVD prevention. This work also led me to design, develop and supervise another related project entitled: 'A Retrospective Cross-Sectional Study Assessing Absolute Cardiovascular Disease Risk Score And Pharmacotherapy At The Time Of Admission In Patients Presenting With Acute Coronary Syndrome Due To Coronary Artery Disease In A Single Australian Tertiary Centre.' I was the senior author and wrote most of the manuscript. This has been published in the BMJ Open on February 8th 2021 and the manuscript is attached in the Appendix. The National Heart Foundation of Australia have issued a letter acknowldeging the health impact of the work I have done during this thesis (see Figure 4A in Appendix).

Since this study was performed, the GP Heart Health Check was introduced by the federal government in April 2019 and is funded under the Medicare Benefits Schedule. It offers specific reimbursement to GPs to carry out absolute cardiovascular risk score assessment on their patients (2). The federal government also introduced the Practice Incentives Program Quality Improvement Incentive in 2019 (3). This is a payment to general practices that participate in quality improvement activities to improve patient outcomes and deliver best practice care. One of the specified improvement measures is the 'Proportion of patients with the necessary risk factors assessed to enable CVD assessment'. Whilst the number of assessments have increased since its introduction, the full impact of these measures are yet to be made clear.'

Acknowledgements

I would like to acknowledge our research governance unit at Sunshine Coast University Hospital, and the support of the Central Queensland Sunshine Coast and Wide Bay Primary Health Network (Dr John Harper, Robb Major and Deidre Ballinger). Also, the help of Rachelle Foreman and Natalie Raffoul of the National Heart Foundation of Australia, in the design of the survey questionnaire. I would also like to thank all of the GPs who participated in this project.

BMJ Open

Cross-sectional survey describing general practitioners' absolute cardiovascular disease risk assessment practices and their relationship to knowledge, attitudes and beliefs about cardiovascular disease risk in Queensland, Australia

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To cite: Greaves K, Smith A, Agostino J, *et al*. Cross-sectional survey describing general practitioners' absolute cardiovascular disease risk assessment practices and their relationship to knowledge, attitudes and beliefs about cardiovascular disease risk in Queensland, Australia. *BMJ Open* 2020;**10**:e033859. doi:10.1136/bmjopen-2019-033859

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-033859).

Received 31 August 2019
Revised 12 May 2020
Accepted 29 May 2020

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ABSTRACT

Objectives To describe general practitioners' (GPs') absolute cardiovascular disease risk (ACVDR) self-reported assessment practices and their relationship to knowledge, attitudes and beliefs about ACVDR.

Design Cross-sectional survey with opportunistic sampling (October–December 2017).

Setting Sunshine Coast region, Queensland, Australia.

Participants 111 GPs responded to the survey.

Primary and secondary outcome measures Proportion of GPs reporting a high (≥80%) versus moderate (60%–79%)/low (<60%) percentage of eligible patients receiving ACVDR assessment; proportion agreeing with statements pertaining to knowledge, attitudes and beliefs about ACVDR and associations between these factors.

Results Of the 111 respondents, 78% reported using the Australian ACVDR calculator; 45% reported high, 25% moderate and 30% low ACVDR assessment rates; >85% reported knowing how to use ACVDR assessment tools, believed assessment valuable and were comfortable with providing guideline-recommended treatment. Around half believed patients understood the concept of high risk and were willing to adopt recommendations. High assessment rates (vs moderate/low) were less likely among older GPs (≥45 vs ≤34 years, age-adjusted and sex-adjusted OR (aOR) 0.36, 95% CI 0.12 to 0.97). Those who answered knowledge-based questions about the guidelines incorrectly had lower assessment rates, including those who answered questions on patient eligibility (aOR 0.13, 95% CI 0.02 to 1.11). A high assessment rate was more likely among GPs who believed there was sufficient time to do the assessment (aOR 3.79, 95% CI 1.23 to 11.61) and that their patients were willing to undertake lifestyle modification (aOR 2.29, 95% CI 1.02 to 5.15). Over 75% of GPs agreed better patient education, nurse-led assessment and computer-reminder prompts would enable higher assessment rates.

Conclusions Although the majority of GPs report using the ACVDR calculator when undertaking a CVD risk assessment, there is a need to increase the actual proportion of eligible patients undergoing ACVDR assessment. This may be achieved by improving GP assessment practices such as GP and patient knowledge of CVD risk, providing sufficient time and nurse-led assessment.

Strengths and limitations of this study

- ► First survey to assess the proportion of eligible patients undergoing absolute cardiovascular disease risk score assessment as self-reported by general practitioners (GPs).
- ► Ability to examine the association between CVD assessment rates by GPs, and GP knowledge, attitudes and beliefs about CVD risk.
- ► Limited to GPs in Queensland, Australia.
- ► Relies on self-reporting by GPs rather than objective measures.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Australia, and its prevention is a national health priority.[1–3] A large proportion of CVD is preventable by appropriate population-level interventions and individual management of risk.[4] The potential benefit of treatments to reduce CVD events are closely related to an individual's absolute or total cardiovascular disease risk (ACVDR).[5 6]

The National Vascular Disease Prevention Alliance (NVDPA) of Australia guidelines recommend calculating risk using the ACVDR Score.[7] Factors included in the risk score are age, gender, smoking, systolic blood pressure,

total cholesterol to high density lipoproten (HDL) ratio and diabetes. A 5-year risk for the development of CVD is calculated and categorised according to whether a patient has low (<10%), moderate (10%–15%) or high (>15%) risk. Certain groups of patients are automatically considered at high risk and do not need to have their risk calculated. For example, those patients with known CVD, who are diabetic and over 60 years of age, or who have a cholesterol equal to 7.5 mmol/L or higher. A version of the risk score calculator is usually embedded in the general practitioner (GP) patient management software or can be accessed directly at the Heart Foundation's website.[8] Patients without prior CVD and a high ACVDR score, or moderate risk with additional risk factors, are recommended to receive lifestyle modification advice and be prescribed both lipid and blood pressure-lowering therapy. However, most Australians at high CVD risk are not receiving recommended combination therapy.[9] This treatment gap is likely due to multiple factors, including lack of assessment by GPs.[9–12] Studies examining ACVDR assessment in general practice report anywhere between 17% and 85% of GPs use risk assessment tools.[9 12 13] However, the actual proportion of eligible patients that have their ACVDR calculated by their GPs is unknown.

The barriers to risk assessment faced by GPs, particularly those based in Europe, are well described.[11 13] These include lack of time to undertake risk assessment, incentives and GP–patient knowledge regarding cardiovascular risk. However, whether these known barriers or other GP characteristics are associated with the proportions of eligible patients undergoing ACVDR score assessment self-reported by GPs in Australia are unknown.

The aims of this study were to describe Australian GPs' self-reported ACVDR assessment practices, and knowledge, attitudes and beliefs about ACVDR; examine associations between ACVDR assessment rates and GP characteristics, and knowledge, attitudes and beliefs about ACVDR; and report on GP ratings of potential barriers and enablers of ACVDR assessment.

METHODS

Study design and population

We undertook a cross-sectional survey with opportunistic sampling of participants. During October–December 2017, the survey was made available to actively practising GPs on the Sunshine Coast region of Queensland in electronic and hard copy format. Distribution lists of GP practices were obtained from the Primary Healthcare Network. The web-based survey was also placed on a Survey Monkey platform, and this link was circulated via email and on social media to GPs. Hard copies of the surveys were also provided to GPs in person to complete the survey at their workplace. Additionally, the survey was distributed at GP education events.

The total number of GPs approached was not measured. Online sharing of the survey web link by GPs meant that practitioners outside the Sunshine Coast region also completed the survey and, provided they were from Queensland, were accepted into the study.

Survey questionnaire

The survey questionnaire was developed from information in the existing literature, previous surveys (online supplementary figure 1) as well from the direct experiences expressed by GPs to the investigators.[12 14–18] This was then refined several times following consultation with two cardiologists (KG and TS), three GPs, two primary healthcare network staff, a senior member of the Heart Foundation and an epidemiologist (RK). The survey used closed-ended questions to collect self-reported information on GP and workplace characteristics (questions 1–8, 16–18) and on perceived ACVDR knowledge (questions 9 and 10) and assessment practices, including a question on the proportion of eligible patients assessed (response categories: all (ie, 100%), 80%–99%, 60%–79%, 40%–59%, 30%–39%, 1%–19%, never (0%), 'I do not assess total CVD risk in general', 'I assess treat each factor individually', 'I am unsure who an eligible patient is for total CVD disease risk assessment' and 'Other'). For information on attitudes, beliefs (question 21.1, 21.4–21.15 and 22.13) and further perceived knowledge (questions 13–15, 20, 21.1 and 21.2) in relation to ACVDR risk assessments, GPs were asked to rate their responses to 15 separate items relating to GP, patient and organisational/structural factors, using a 7-point Likert scale ranging from 'strongly disagree' to 'strongly agree'. In addition, GPs were asked to rate potential barriers and enablers to performing ACVDR assessments, using a 7-point Likert scale (question 22.1–22.12). The full survey can be accessed in the online supplement (online supplementary figure 1). Information on the time taken explaining the meaning of the risk score to patients (question 23) and also referral practices (question 24) were also recorded.

Analysis

Assessment practices were described in terms of number and proportion (%) of GPs. For the analysis, we dichotomised assessment rates—the main outcome variable—into high (≥80% eligible patients receiving ACVDR assessment) versus moderate (60%–79%)/low (<60%) and proportion agreeing into yes (includes those who reported 'strongly agree', 'agree' and 'agree somewhat') or no ('strongly disagree', 'disagree', 'disagree somewhat' or 'undecided') for statements pertaining to knowledge, attitudes and beliefs about ACVDR and proposed barriers and enablers. We used logistic regression to quantify the association between GP characteristics, knowledge, attitudes and beliefs and ACVDR assessment rates, reporting both crude and age-adjusted and sex-adjusted ORs with 95% CIs. For several of the variables on GP characteristics, response categories were combined due to small numbers.

A sensitivity analysis was performed whereby the assessment rate variable was recategorised as high/moderate

combined (ACVDR assessed in ≥60% of eligible patients) versus low. Stata V.15.1 was used for statistical analyses.

A verbal and/or written explanation of the purposes of the survey was given to GPs prior to completing the survey. No identifying details of participants were recorded. All data reported were aggregate. This study was considered to be low risk. The ethics committees did not require a consent form to be signed by participants as completion of the survey was considered as consent to participate.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination of our research.

RESULTS

GP characteristics and ACVDR assessment practices

A total of 111 GPs responded to the survey of whom 78 (70%) were based on the Sunshine Coast, which represents 13% of the approximately 600 GPs registered on the Sunshine Coast. Fifty-three per cent were male and 43% were aged ≥45 years (see table 1).

Nearly all GPs (108/111, 96%) reported being aware of ACVDR assessment and around half (46%) had heard of the Guidelines for the Management of Absolute CVD Disease Risk as issued by the NVDPA.

Fifty (45%, 95% CI 36% to 55%) GPs were high assessors with 19 (17%) reporting assessing 100% of eligible individuals; 28 (25%, 95% CI 17% to 34%) GPs were moderate assessors and 33 (30%, 95% 21% to 39%) low assessors. Within the low assessment group, six (5% of all GPs respondents) assessed <20% eligible patients; six (5%) were unsure of who an eligible patient was, did not assess CVD risk or treated risk factors individually; overall. this was equivalent to 1 in 10 GPs. The eight (7%) written responses in the 'Other' section were categorised as low assessors. The full range of assessment rates is shown in table 2. Most GPs (78%) used the Australian ACVDR calculator, either alone (72%) or in combination with another risk system (6%), with a small minority using Q-risk (4%). Nine per cent used either their own clinical judgement, did not use a risk score system or did not know. The remaining (9%) used other algorithms. Nearly half (48%) of GPs spend between 5 min and 9 min explaining the score, 28% 0–4 min and 15% 10–15 min.

Referral patterns of GPs for lifestyle modification are shown in online supplementary table 1. The most commonly referred to practitioners are dietitians (76%), exercise physiologists (68%) and creation of a chronic disease management plan (60%).

Table 3 shows crude and age-adjusted sex-adjusted ORs for the association between GP characteristics and high assessment rates. Increasing age and years worked were associated with lower assessment rates, but only age remained associated in the adjusted analysis, with older GPs less likely to assess a high proportion of patients (aOR ≥45vs ≤34 years=0.36, 95% CI 0.12 to 0.97).

Table 1 GP characteristics for high and moderate/low assessors

	High assessors % (n), n=50	Moderate/low assessors % (n), n=61	Total N (%), n=111
Age range (years)			
≤34	26 (13)	16 (10)	23 (21)
35–44	46 (23)	28 (17)	40 (36)
≥45	28 (14)	57 (34)	48 (43)
Gender			
Female	62 (31)	46 (28)	59 (45)
Male	36 (18)	52 (32)	50 (53)
Intersex/ indeterminate	50 (1)	50 (1)	2 (2)
Years worked as GP			
≤5	44 (22)	21 (13)	35 (32)
6–15	30 (15)	36 (22)	37 (33)
≥16	26 (13)	43 (26)	39 (35)
Employment status			
Full time	60 (30)	61 (37)	67 (60)
Part time/casual	40 (20)	39 (24)	44 (40)
Hours worked per week			
≤29	16 (8)	18 (11)	19 (17)
30–39	40 (20)	20 (12)	32 (29)
40	20 (10)	18 (11)	21 (19)
≥41	24 (12)	44 (27)	39 (35)
Number of GPs in workplace			
<10	62 (31)	59 (36)	67 (60)
≥10	30 (15)	38 (23)	38 (34)
Work at >1 practice	8 (4)	4 (2)	6 (5)
Role in practice			
Registrar/in training	20 (10)	8 (5)	15 (14)
Contractor/ sessional/ retainer/salaried	66 (33)	70 (43)	76 (68)
Partner/principal	14 (7)	21 (13)	20 (18)

High assessors assessed CVD risk scores in ≥80% of their eligible patients. Moderate and low assessors assessed absolute CVD risk in ≤79% of their eligible patients. Total questionnaires completed 111. No missing data.
CVD, cardiovascular disease; GP, general practitioner.

GP knowledge, attitudes and beliefs about ACVDR assessment and associations with assessment rates

Around 1 in 10 GPs (11%) were not aware that ACVDR assessment should be performed in all eligible patients.

Table 2 Assessment rates for CVD risk by GPs in eligible patients

In what percentage of eligible patients do you assess total CVD risk?	Number	Per cent
100%	19	17
80%–99%	31	28
60%–79%	28	25
40%–59%	6	5
20%–39%	9	8
1%–19%	5	5
I do not assess CVD risk	2	2
I assess and treat each risk factor individually	2	2
I am unsure who an eligible patient is	1	1
Other	8	7
Total	111	100

'Other': written text responses from GPs, which were a combination of assessing each factor individually and using ACVDR risk calculator; different age category and >1 risk factor.
ACVDR, absolute cardiovascular disease risk; CVD, cardiovascular disease; GPs, general practitioners.

GPs were asked how regularly they should reassess an individual's ACVDR if low, moderate or high risk according to NVDPA risk guidelines (7). The proportions of GPs that correctly answered were 13 (11%), 56 (42%) and 12 (11%), respectively. GPs were asked about the age range at which patients became eligible for ACVDR assessment: 48 (43%) answered correctly and the remaining were incorrect (10%) or did not respond (47%).

A high proportion of GPs (>85%) reported they knew how to use ACVDR assessment tools, how to proceed after assessment, believed ACVDR assessment valuable and were comfortable with prescribing dual medications for high and moderate risk patients (table 4). A third of GPs agreed ACVDR assessment was accurate in the elderly, and one in eight GPs referred patients for a calcium score. The questions relating to GP perceived knowledge, attitudes and beliefs can also be found in table 4.

Around half of GPs believed their patients understood the concept of high risk and would adhere to medications (59%) and would participate in lifestyle modification services (52%). The majority of GPs (77%) agreed there was sufficient time to undertake ACVDR assessment during a routine appointment, while 29% reported opportunistic assessments were difficult. Almost 40% of GPs agreed there was a lack of incentives to undertake ACVDR assessment, and 20% reported cholesterol results were not available in those who needed ACVDR assessment.

Several factors relating to GPs' self-reported perceived knowledge, attitudes and beliefs were associated with assessment rates. Lack of knowledge that assessment was recommended in all eligible patients was associated with lower assessment rates (OR 0.09, 95% CI 0.1 to 0.76; aOR 0.13, 95% CI 0.02 to 1.11). A high assessment rate (vs moderate/low) was also associated with knowledge of how to proceed after the ACVDR assessment (OR 8.47, 95% CI 1.03 to 69.38; aOR 7.35, 95% CI 0.76 71.35). A high (vs moderate/low) assessment rate was associated with belief that: there was sufficient time to do the assessment (aOR 3.79, 95% CI 1.23 to 11.61); their patients would participate in lifestyle modification services (aOR 2.29, 95% CI 1.02 to 5.15); and their patients understood the concept of being at high risk and adhere to medications (aOR 2.00, 95% CI 0.88 to 4.58). High assessors were more likely to take a longer time with their patients explaining ACVDR (aOR 3.95, 95% CI 1.33 to 11.7). High assessment rates were less likely among GPs who agreed it was difficult to opportunistically assess ACVDR during routine consultations (aOR 0.42, 95% CI 0.16 to 1.11) and also agreed that the ACVDR score estimated risk over too long a time (aOR 0.24, 95% CI 0.07 to 0.78). Clinical practice software, inbuilt calculator availability and the use of these tools were not associated with assessment rates. Views regarding lack of incentives, funding and effective lifestyle modification services were also not associated with assessment rates (table 4).

Perceived barriers and enablers to ACVDR assessment

Almost 80% of GPs agreed better consumer education for patients could increase uptake, and that nurses could prescreen eligible patients prior to their GP appointment (table 5), with 71% also believing practice nurses could undertake assessment themselves. Three-quarters felt computer prompt reminders would be helpful. Over 70% felt a recall of all eligible patterns in their registry would be effective, and that adequate funding or incentives would increase uptake. Sixty-five per cent agreed dedicated assessment time in their schedule would increase assessments, and 62% reported the best way to undertake assessments was opportunistically. The questions relating to enablers can also be found in table 5.

Sensitivity analysis

The analyses examining associations between assessment rate and GP characteristics, knowledge attitude and beliefs were repeated with the binary outcome variable redefined as 'high/moderate assessors' (risk scores assessed in ≥60% eligible patients, 70% of GPs) versus low assessors (<60% eligible patients, 30% of GPs) and did not differ materially from the main analyses.

DISCUSSION

This study on self-reported practices of regional GPs on CVD risk showed the vast majority use ACVDR assessment, but less than half assess ≥80% of eligible patients, and 1 in 10 is assessing ACVDR in a low proportion of their patients<20%) or not at all. GPs who are older, have a lower knowledge of ACVDR guidelines and/or believe

Table 3 Crude and age-adjusted sex-adjusted ORs for the association between GP and practice characteristics, and high versus moderate/low rates of assessment for absolute CVD risk (ACVDR)

Independent variable	Percentage per category (n) that are high assessors	Crude OR	95% CI	Ageadjusted and sex-adjusted OR	95% CI	P value
Age range (years)						
≤34	57(13)	1.0	–	–	–	0.03
35–44	58 (23)	1.04	0.37 to 2.93	1.07	0.36 to 2.90	–
≥45	29 (14)	0.31	0.11 to 0.89	0.36	0.12 to 0.97	–
Gender						
Female	53 (31)	1.0	–	–	–	0.25
Male	36 (18)	0.51	0.24 to 1.10	0.72	0.34 to 1.54	–
Years worked						
≤5	63(22)	1.0	–	1.0	–	0.08
6–15	41(15)	0.40	0.16 to 1.04	0.23	0.15 to 1.46	–
≥16	33(13)	0.30	0.11 to 0.77	0.49	0.11 to 2.15	–
Employment status						
Full time	45 (30)	1.0	–	1.0	–	0.80
Not full time	45 (20)	1.02	0.48 to 2.21	0.90	0.40 to 2.02	–
Hours worked/week						
≤29	42 (8)	1.0	–	1.0	–	0.27
30–39	63 (20)	2.29	0.72 to 7.30	2.29	0.63 to 6.84	–
40	48 (10)	1.25	0.36 to 4.36	1.36	0.35 to 4.90	–
≥41	31 (12)	0.61	0.20 to 1.90	0.86	0.22 to 2.32	–
Number of GPs in workplace						
≤4	44 (8)	1.0	–	1.0	–	0.41
5–9	47 (23)	1.11	0.37 to 3.28	1.14	0.36 to 3.61	–
10–19	44 (11)	0.98	0.29 to 3.33	1.44	0.39 to 5.27	–
≥20	31 (4)	0.56	0.12 to 2.49	0.80	0.16 to 3.97	–
Role in practice						
Registrar/in training	68 (10)	1.0	–	1.0	–	0.58
Contractor/sessional/retainer/salaried	43 (33)	0.38	0.12 to 1.23	0.49	0.15 to 1.78	–
Partner/principal	35 (7)	0.27	0.07 to 1.11	0.51	0.11 to 2.61	–
ACVDR risk score						
Used	45 (36)	1.0	–	1.0	–	0.22

Continued

Table 3 Continued

Independent variable	Percentage per category (n) that are high assessors	Crude OR	95% CI	Ageadjusted and sex-adjusted OR	95% CI	P value
Other score used/not used	45 (14)	0.99	0.41 to 1.67	0.54	0.20 to 1.43	–
Type of practice clinical software used						
Medical director	57 (13)	1.0	–	1.0	–	0.37
Best practice	46 (32)	0.65	0.25 to 1.67	0.68	0.25 to 1.83	–
Not applicable	28 (5)	0.30	0.08 to 1.11	0.38	0.09 to 1.50	–
Inbuilt calculator availability						
Available	47 (37)	1.0	–	1.0	–	0.60
Not available/unsure	39 (13)	0.72	0.31 to 1.64	0.79	0.32 to 1.92	–
Use of inbuilt calculator						
Yes	46 (30)	1.0	–	1.0	–	0.85
No	44 (7)	0.91	0.30 to 2.73	0.89	0.29 to 2.81	–
Knowledge of correct age eligible for assessment						
Incorrect/missing	41 (26)	1.0	–	1.0	–	0.90
Correct	50 (24)	0.70	0.67 to 3.03	1.06	0.46 to 2.42	–
Time spent explaining ACVDR risk to patient						
0–4 mins	24 (27)	1.0		1.0		0.02
>5 mins	58 (65)	3.84	1.37 to 10.7	3.63	1.26 to 10.4	–

High assessors assessed cardiovascular disease risk scores in ≥80% of their eligible patients. Moderate/low assessors assessed ACVDR risk in ≤79% of their eligible patients. Total questionnaires completed 111. No missing data except 'time spent explaining ACVDR risk to patient': never undertake/other/missing n=20 (18%).
ACVDR, absolute cardiovascular disease risk; GPs, general practitioners.

Table 4 GP knowledge, attitudes and beliefs in relation to absolute CVD risk (ACVDR) assessment: percentage agreeing with statements overall, and agreeing by ACVDR assessment rates (high vs moderate/low assessors), and associated crude and age-adjusted and sex-adjusted ORs

	Agree (%)	High assessors (%)	Moderate/ low assessors (%)	Crude OR	95% CI	Age-adjusted and sex-adjusted OR	95% CI	P value
GP factors								
I know how to use total CVD assessment tools	90	96	88	3.1	0.61 to 15.68	2.31	0.40 to 13.50	0.35
I know how to proceed after the total CVD risk assessment	89	98	85	8.47	1.03 to 69.38	7.35	0.76 to 71.35	0.09
The total CVD risk assessment allows for accurate calculation of CVD risk in elderly patients	32	33	32	1.05	0.47 to 2.35	1.21	0.51 to 2.88	0.66
The total CVD risk assessment estimates risk over too long a time period	18	10	25	0.34	0.11 to 1.02	0.24	0.07 to 0.78	0.02
I prefer to refer patients for a calcium score	12	10	13	0.74	0.23 to 2.42	1.09	0.30 to 4.03	0.81
I am comfortable with prescribing blood pressure and lipid lowering medications for patients identified at high total cardiovascular risk	97	98	100		Only 1 GP disagreed so no result	–	–	–
I am comfortable with prescribing blood pressure and lipid lowering medications for patients identified at moderate total cardiovascular risk for whom despite lifestyle changes have not improved	89	94	88	2.03	0.49 to 8.29	2.87	0.64 to 12.88	0.17
I believe the total CVD risk assessment is a valuable tool for decision making	86	95	93	1.56	0.27 to 8.90	1.48	0.21 to 10.62	0.70
Patient factors								
Patient's understand the concept of being at high risk of a chronic disease and are adherent to prescribed medications	59	69	52	2.12	0.96 to 4.68	2.00	0.88 to 4.58	0.10
Patients are willing to participate in lifestyle modification services	52	63	45	2.10	0.97 to 4.55	2.29	1.02 to 5.15	0.05
Organisational and structural factors								
I think there is sufficient time during a routine appointment to calculate total CVD risk	77	90	70	3.77	1.28 to 11.08	3.79	1.23 to 11.61	0.02
There are a lack of incentives for me to perform total CVD risk assessments	39	41	38	1.11	0.51 to 2.40	1.15	0.51 to 2.61	0.74

Continued

Table 4 Continued

	Agree (%)	High assessors (%)	Moderate/ low assessors (%)	Crude OR	95% CI	Age-adjusted and sex-adjusted OR	95% CI	P value
Total CVD risk assessments are difficult to incorporate opportunistically during patient consultations	26	16	35	0.36	0.14 to 0.91	0.42	0.16 to 1.11	0.08
Total cholesterol and HDL results are often not available for patients requiring total CVD risk assessment	20	18	18	1.00	0.38 to 2.66	0.93	0.33 to 2.58	0.88
There are a lack of effective lifestyle modification services to refer on to	59	65	57	1.44	0.66 to 3.14	1.23	0.54 to 2.82	0.62
There is lack of funding for lifestyle modification services to refer on to	18	84	75	1.71	0.66 to 4.45	1.39	0.51 to 3.81	0.52

High assessors assessed cardiovascular disease (CVD) risk scores in ≥80% of their eligible patients. Moderate/low assessors assessed ACVDR in ≤79% of their eligible patients. Total questionnaires completed n=111. Data were incomplete in two (2%) patients, except for the question 'I believe the total CVD risk assessment is a valuable tool for decision making', which had nine (8%) missing. Percentage agreeing=proportion of GPS who 'strongly agreed', 'agreed' or 'somewhat agreed'/total GPs who responded × 100.
GPs, general practitioners.

their patients lack understanding of CVD risk have lower assessment rates. GPs with higher assessment rates are more likely to report having sufficient time in consultations and spend more time explaining ACVDR risk to their patients. There was high agreement among GPs that actions that would enable ACVDR assessment were better patient education, nurse-led assessment and computer-reminder prompts.

Table 5 Potential enablers to increase absolute CVD risk assessments: percentage of GPs agreeing with statements

	Agree (%)
Better consumer education for patients about having their total CVD risk checked could increase uptake of assessments.	86
Patients eligible for a total CVD risk assessment could be prescreened by the practice nurse prior to their GP appointment.	86
Computer prompt reminders for patients due for a total CVD risk assessment could increase uptake.	82
If adequate government funding/incentives were available for completing total CVD risk assessments, I would be more likely to complete these assessments.	78
Practice nurses are well suited to perform total CVD risk assessments.	78
A recall of all eligible patients in the GP registry due for a total CVD assessment would be an effective method of increasing uptake.	77
If I was allocated dedicated screening time in my schedule, I could complete more total CVD risk assessments.	73
GPs should continue to be the health professional that completes total CVD risk assessments.	69
The best way for me to complete total CVD risk assessments is opportunistically.	70
Point of care testing for cholesterol and HDL would enable more total CVD risk assessments.	63
Total CVD risk assessments performed within a workplace setting could be an effective means of increasing uptake.	63
If appointment time slots were increased, this could enable more total CVD risk assessments.	61

Total n=111, 8%–10% missing for each statement. Percentage agreement=proportion of GPs who 'strongly agreed', 'agreed' or 'agreed somewhat'/total GPs who responded × 100.
CVD, cardiovascular disease; GPs, general practitioners.

There are limited data published in Australia and internationally on ACVD assessment coverage in general practice. A 2012 survey of 806 physicians across 12 European countries found 85% reported following at least one set of CVD risk guidelines, but there was no indication as to what proportion of their eligible patients underwent risk assessment.[13] The 2006 National (USA) Research network Survey on CVD risk assessment found 92% of GPs reported 'usually' or 'always' assessing for CVD risk factors; however, only 17% used a risk calculator.[19] Our study is consistent with these findings in that although the majority of GPs were aware of the absolute CVD risk concept, less than half had heard of the NVDPA guidelines and 11% were unaware CVD risk assessment should be carried out in all eligible patients. However, in our study, around 90% of GPs reported using a risk calculator of some kind. To our knowledge, our study is the first in Australia on self-reported assessment rates for CVD risk among individual GPs, finding they are relatively low. Although the AusHEART study reported almost 90% of GPs provided an estimate of absolute risk, the provision of this estimate was a mandatory part of the protocol.[12]

A lack of knowledge by GPs is known to be a barrier to the use of guidelines. The EURIKA study reported 12% of GPs did not use guidelines, of whom 28% cited 'not knowing the guidelines' as the reason why.[13] A study of 25 Australian GPs reported that those not familiar with the guidelines or use of the tools did not calculate CVD risk.[15] In our study, incorrect answers on patient eligibility and assessment intervals for risk scoring were associated with lower assessment rates. Those who knew how to use and proceed after using the guidelines had high assessment rates. Previous studies have documented that a small proportion of GPs still base their assessment of CVD risk on a single risk factor and this is also consistent with our findings.[20] The difference between the number of GPs who had heard of the ACVD risk guidelines (96%) and who had heard of the NVDPA (45%) is perhaps not unexpected. While the NVDPA guidelines form the basis of CVD risk assessment in Australia, GPs may get advice from preventive health guidelines such as the RACGP Red Book, which includes the NVDPA algorithm.

Patient knowledge and behaviour is also known to influence a GP's assessment of CVD risk. A systematic review on GP perspectives of CVD prevention found lack of patient motivation for behavioural change and a capacity for lifestyle change to be important practice influencers.[9] Our study revealed this too, and most GPs believed better consumer education for patients would increase CVD risk assessment.

Time availability is also known to be a significant factor affecting ACVDR assessment and is consistent with our findings that GPs who felt there was sufficient time for assessment had higher assessment rates.[13 21]

There was high agreement on a number of possible strategies to increase assessment. These included preassessment of patients prior to their appointment, which could be nurse led, and recall of known high-risk patients not appropriately treated. Nurse-led interventions have been shown to be successful in cardiovascular care.[22]

To encourage increased uptake of ACVDR, the Australian government introduced a Heart Health Assessment, which requires ACVDR assessment, to the Medicare Benefits Schedule (MBS) in April 2019.[23] While our study preceded the new MBS Heart Health Assessment, this new MBS item addresses some enablers identified in our study that may increase ACVDR assessment such as preassessment by practice nurses and a modest financial incentive.[23] However, our results indicate that consumer education needs to accompany this new item.

This study was limited to GP practices in Queensland with opportunistic sampling of a small percentage of GPs predominantly from the Sunshine Coast, which itself has different demographics to other areas within Australia. Therefore, its applicability to other regions and countries should be considered. Our study also relies on GPs self-reporting rather than objective measurements of behaviour, which is an inherent problem with questionnaire-based surveys and should be taken into account when interpreting the results. It is also worth noting that apart from age eligibility for screening, our survey measured GPs perceived rather than factual knowledge of CVD risk assessment. Another point is that there is likely bias in the self-reported *assessment rates* (probably overestimated), and hence these may not be generalisable to the GP population. However, representativeness is not necessary for valid internal comparisons, that is, our estimates of the associations between factors (GPs knowledge, attitudes and beliefs) and assessment rates are internally valid, and thus also our conclusions regarding barriers and enablers. We did not define the eligible population for ACVDR assessment in the survey as we wished to understand GPs knowledge on this topic. Only 43% answered correctly on the age patients became eligible for assessment. It is therefore likely that a proportion of GPs may be assessing the incorrect patients. However, we would not expect this fact to alter the conclusions of our study given it was not the purpose of the study to assess what proportion of eligible patients are actually assessed in primary care (this would obviously require a different study design), rather the purpose was to better understand enablers and barriers to assessment (by examining factors associated with assessing/not assessing patients deemed eligible for assessment).

CONCLUSION

This study showed that although the majority of GPs report using the ACVDR calculator when undertaking a CVD risk assessment, there is a need to increase the actual proportions of eligible patients undergoing ACVDR assessment. This might be achieved by improving GP assessment practices, including through increasing GP and patient knowledge of CVD risk, nurse-led assessment and providing sufficient time for GP ACVDR assessment. Addressing these issues could lead to increased

identification and treatment of at-risk patients and the reduction of CVD.

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Acknowledgements The authors would like to acknowledge the help of Rachelle Foreman of the National Heart Foundation of Australia, Dr John Harper, Robb Major and Deidre Ballinger of Central Queensland, Wide Bay and Sunshine Coast Primary Health Network, in the design of the survey questionnaire.

Contributors All authors made substantial contributions to the conception or design of the work; the acquisition, analysis and interpretation of data for the work; KG drafted the work and gave final approval of the version to be published. All authors revised it critically for important intellectual content and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The survey was approved by the human research ethics committees of the Royal Brisbane and Women's Hospital (HREC/17/QRBW/98) and the Australian National University (Protocol 2017/600).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No additional data available.

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CHAPTER 5

DATA ANALYSIS

Prevalence of coronary microvascular dysfunction in patients being investigated for chest pain in an outpatient setting, and association with typical angina symptoms: a cross-sectional study.

Table of Contents

List of Figures and Tables

Abstract

Objective Coronary microvascular dysfunction (CMD) is thought to be the cause of typical angina in patients with chest pain and unobstructed coronary arteries but studies investigating this have failed to show an association. In the same population our study investigated: 1) the prevalence of CMD; 2) whether the presence of global or regional CMD is associated with typical angina; 3) whether this association was modified sex.

Methods This cross-sectional study recruited consecutive patients attending cardiology clinics with chest pain and unobstructed coronary arteries on CT angiography. Myocardial blood flow reserve (MBFR) was assessed using vasodilator myocardial contrast echocardiography, and CMD was defined as a MBFR <2.0. Global MBFR was calculated as the average MBFR of all segments of the left ventricle. Regional MBFR was calculated as the average MBFR of the segments corresponding to the left ($MBFR_L$) and right coronary artery ($MBFR_R$) territories. Chest pain was classified as either typical angina, defined according Rose Angina Questionnaire criteria, or non-specific chest pain. Univariate logistic regression was used to quantify the association between a CMD and typical angina. Multivariate logistic regression was performed with age, sex and diabetes entered into the model. To examine effect modification by sex, the CMD-angina relationship was analysed separately in men and women, and used the likelihood ratio (LR) test to test for homogeneity. The same analyses were repeated using regional CMD derived from the left and right coronary artery territories.

Results 183 participants, mean age 60±9.6 years (53% male), were recruited. Typical angina was present in 34% (95% CI: 28-42%) of participants. Mean global MBFR

(mean±SD) was 2.20(2.12-2.27) and 70(38%) had global CMD. There was no significant association between global CMD and angina, overall [aOR 1.72, (95% CI:0.91-3.23), p=0.09], in women [aOR 1.89, (95% CI:0.75-4.74), p=0.29], or in men [aOR 1.60, 95% CI: 0.67-3.81, p=0.29]. CMD in the right coronary artery territory was associated with angina [aOR 3.76(1.97-7.18), p<0.001], in both women [aOR 4.30(1.67-11.1) p=0.003)], and men [aOR 3.40(3.39-8.28)], p=0.007) (test for homogeneity, p= 0.665). CMD in the left coronary artery territory was not associated with angina in women [aOR 1.96(95% CI 0.82-4.67), p=0.13] or men [aOR 1.23(95% CI 0.48-3.26), p=0.64].

Conclusion This study demonstrated that a third of patients referred to clinics with chest pain and unobstructed coronary arteries have CMD. Global CMD was not associated with typical angina but the presence of CMD in the right coronary artery territory was associated with angina in both males and females. The strength of this association was similar in men and women**.**

My role

The data from this study was collected between 2011 and 2013 when I was a consultant at Poole Hospital in the UK. I designed the original study, gained funding and supervised the ethics submission, patient recruitment, the experiments, and collection of the data. During my time as a MAE student, I undertook the data analysis, and carried out all of the data analysis and write-up of the manuscript.

Lessons learnt

This experiment was conducted 10 years ago and the design was 2 years prior to this. By reflecting what I have learnt in the MAE program I was able to identify many weaknesses in the design of the project which were not clear to me before. These included the importance of a causal diagram and data analysis plan, which I now undertake before all research projects I am involved in. Even though a cross-sectional design is not designed to determine causality, the causal diagram helped me understand that patients with chest pain should be the outcome variable in the analysis, and CMD the exposure, given the interest was in quantifying and comparing the prevalence of typical angina in people with and without CMD, rather than the other way around. The diagram also helped to determine what variables I should, and should not adjust for, in the analysis. I also realised the limitations of single centre physiological studies and their generalisability, in particular considering issues around selection bias. For future studies I will be more aware of my target population (those with chest pain), the population accessible to me (clinics), the sampling method used (consecutive patients) and the actual participants

that consent to participate. I also learnt how to use Stata which was extremely useful for the data analysis I carried out in my epidemiological project chapter ('A Cross-Sectional Survey Describing General Practitioners' Absolute Cardiovascular Disease Risk Assessment Practices and their Relationship to Knowledge, Attitudes and Beliefs about Cardiovascular Disease Risk in Queensland, Australia'), as well as for future work.

Public health impact

The chapter prepared is in a draft manuscript style with the intent to publish in a peer-reviewed journal. Coronary microvascular dysfunction has prognostic importance as its presence is associated with increased cardiovascular mortality. The findings from this study are hypothesis generating and will stimulate other investigators to consider in their study designs how the presence of CMD in the different parts of the heart may be important in development of angina in patients with normal coronary arteries. This includes further research into the mechanisms and neural pathways involved in of cardiac nociception and the brain-heart interaction.

Acknowledgements

I am grateful to the support and guidance from Associate Professor Rosemary Korda, Dr Jason Agostino, Dr. Chris Anstey and Dr. Jennifer Welsh in this project.

Funding

The work was funded by the Poole Hospital Cardiology Research fund.

List of abbreviations

CAD: coronary artery disease

CMD: coronary microvascular dysfunction

CMD_L: coronary microvascular dysfunction in the left coronary artery territory

CMD_R: coronary microvascular dysfunction in the right coronary artery territory

CT: computed tomography

CTA: computed tomography coronary angiography

ECG: electrocardiogram

MBF: myocardial blood flow

MBFR: myocardial blood flow reserve

$MBFR_L$: myocardial blood flow reserve in the left coronary artery territory

$MBFR_R$: myocardial blood flow reserve in the right coronary artery territory

MCE: Myocardial contrast echocardiography

MVA: microvascular angina

PET: positron emission tomography

Introduction

Chest pain presentations represent 1.5% of all GP consultations and 6% of all emergency department attendances in the UK (1, 2). Despite this, the vast majority of chest pain patients have either normal or non-obstructive (<50% stenosis) coronary artery disease (3). These patients with chest pain and unobstructed coronary arteries often have recurrent chest pain requiring repeated use of healthcare facilities and represent a significant burden to the healthcare system (3, 4). A significant proportion of chest pain and unobstructed coronary arteries patients have been found to have coronary microvascular dysfunction (CMD) especially in women (4, 5). It is postulated that CMD may be the cause of a specific type of chest pain symptom called angina. Angina is present when the following three symptom characteristics are all present: 1) chest pain, 2) chest pain precipitated by physical exertion, and 3) chest pain relieved by rest, or the use of nitrates, within 5 minutes (11). CMD is present when the arterioles in the myocardial microvasculature show an impaired ability to dilate and increase myocardial blood flow in response to increased oxygen demand (6). The resultant ischemia is postulated to cause angina, which in the context of unobstructed coronary arteries and the presence of CMD is called 'microvascular angina' (MVA) (5). CMD also has prognostic importance as its presence is associated with increased cardiovascular and all-cause mortality (7, 8). The concept of MVA originated from a number of studies in which CMD was demonstrated in small, highly selective groups of patients with angina, unobstructed coronary arteries on angiography, and evidence of myocardial ischemia

on exercise electrocardiography testing or other functional imaging, when compared with age- and sex-matched controls (9, 10).

Microvascular angina is a recognized disease entity and European Society of Cardiology guidelines recommend that patients with symptoms of typical angina, unobstructed coronary arteries and CMD on vasodilator testing should be considered to have microvascular angina (MVA) (11). The Coronary Vasomotion Disorders International Study Group recently has also published a set of criteria for the international standardization for the diagnostic criteria for microvascular angina (12). Suspected MVA may be diagnosed when symptoms of myocardial ischemia are present such as effort angina, absence of obstructive coronary artery disease (<50% diameter reduction) on computed tomography (CT) or invasive coronary angiography, and evidence of impaired coronary microvascular function.

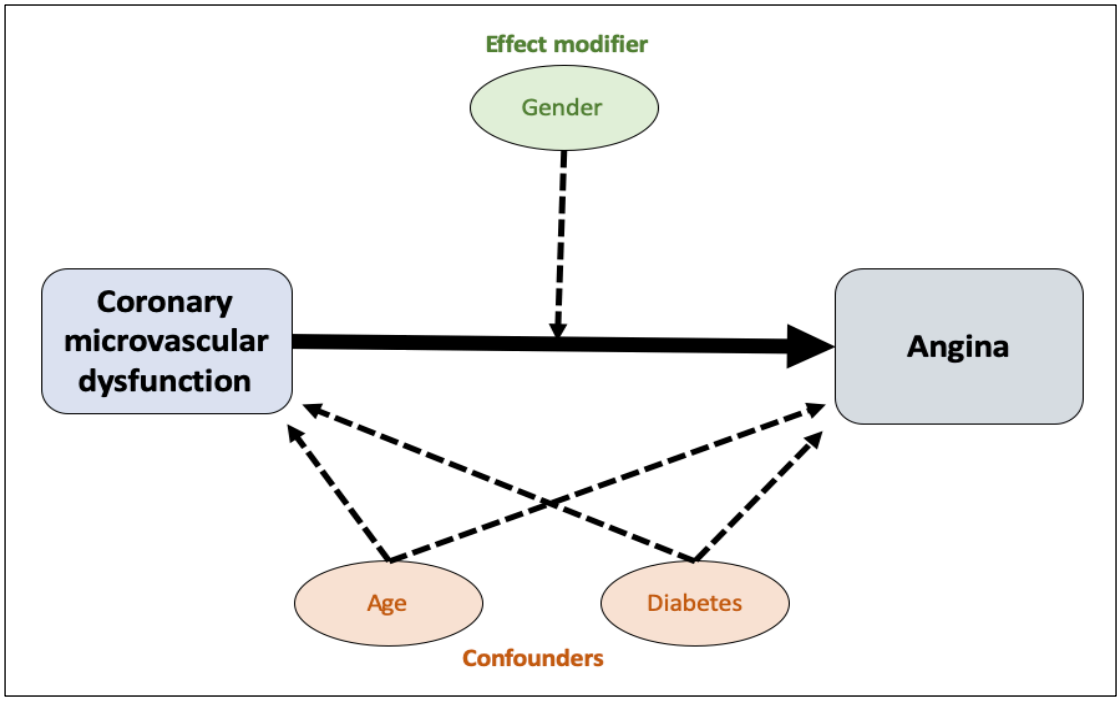
Whilst there is evidence showing that CMD is common in patients with chest pain and unobstructed coronary arteries, it is not clear whether this association is because such patients also tend to have a greater prevalence of factors known to affect microvascular function (8). Studies examining whether CMD is causative of angina have so far failed to show a convincing link (13, 14). One recent study used symptoms as the outcome variable and looked at whether worsening CMD was more prevalent in symptomatic versus asymptomatic women (15). They initially found a significant association but this disappeared if other risk factors such as sex, hypertension and smoking were entered into the model.

Methods used to assess CMD include positron emission tomography (PET), and transthoracic Doppler echocardiography (8, 15). Transthoracic Doppler echocardiography assesses the relative change in blood flow in a single coronary artery and assumes that this is representative of the whole myocardium (16). However, CMD rather than being homogenously present throughout the whole myocardium, may be present in a patchy or heterogenous distribution (16). It is therefore possible that a 'global' or 'averaged' measurement of whole myocardial blood flow, or flow confined to a single territory or region (transthoracic Doppler echocardiography), may miss regional myocardial ischemia that triggers chest pain. Myocardial contrast echocardiography (MCE) is an established technique used in the non-invasive quantification of myocardial blood flow reserve (MBFR) and is used to assess microvascular function (17). This method assesses myocardial blood flow through direct visualisation of the different myocardial segments, microvascular function can be assessed at a both regional and whole-of-myocardium (global) level.

The neural pain pathway from heart to cerebral cortex is highly complex and the perception of angina is influenced by multiple factors such as age and diabetes (18-20). It is well known that the prevalence of angina is higher in women compared to men but the reasons for this are not clear (29). Gender is known to affect the perception of chest pain (21, 22). This could be an important effect-modifier in the context of CMD-induced ischemia causing anginal chest pain (Figure 1). Increasing age and diabetes, both directly affect coronary microvascular function yet both these factors also independently affect chest pain perception. For example, just over 1 in 5 patients with type 2 diabetes have

myocardial ischemia without symptoms of angina (30). Elderly patients suffering myocardial infarction do not present with chest pain but rather non-specific symptoms of unwellness (ochiai). As such these two factors are considered as confounders in the causal diagram linking CMD and angina. Smoking and hypertension, whilst both risk factors for the development of coronary artery disease and coronary microvascular function, do not lie on the casual pathway between angina caused by CMD, in the context of unobstructed coronary arteries (15).

Figure 1. Causal diagram of coronary microvascular dysfunction and angina



This study estimated the prevalence of CMD in patients being investigated for chest pain in an outpatient setting and have unobstructed coronary arteries. This study also investigated whether the presence of either global or regional CMD was associated with typical angina, and whether this relationship was modified by sex.

Methods

Study design and study population.

This was a single centre, cross-sectional study carried out at Poole Hospital NHS Foundation Trust, UK. We recruited consecutive patients aged 30-80 years attending cardiology outpatients (Jan 2011-March 2013) for the investigation of stable chest pain suggestive of myocardial ischemia due to coronary artery disease (CAD) who were also referred for diagnostic CT coronary angiography (CTA). Those with unobstructed coronary arteries underwent transthoracic echocardiography. Unobstructed CAD was defined as a quantitatively measured luminal diameter stenosis <50%.(8) Patients were excluded if they had ≥50% luminal diameter narrowing, known ischemic or valvular heart disease, left ventricular hypertrophy or an ejection fraction <55%, poor image quality, withdrew consent, or an adverse reaction during the MCE or CTA. The remaining patients underwent MCE. Patient demographics were documented following review of patient health records.

Ethics

The study complies with the Declaration of Helsinki and was approved by the South West 4 research ethics committee (H0102/78) of the NHS National Research Ethics Service, UK. All participants provided written informed consent.

Outcome assessment

Following enrollment, patients completed a questionnaire based on the Rose Angina chest pain questionnaire administered by the principle investigator (23). Patients were classified as presenting with either typical angina or non-specific chest pain. Typical angina was present if all four of the following criteria were present: 1) chest discomfort, 2) chest discomfort precipitated by physical exertion, 3) chest discomfort relieved by rest or glyceryl trinitrate, and 4) chest discomfort resolved within 10 minutes. If any of these criteria were absent then the patient was categorised as being in the non-specific chest pain group.

CT angiography imaging and image analysis

CTA is a non-invasive method by which the coronary arteries can be imaged using X-rays and radiographic dye injection through a peripheral arm vein. The patient lies on the CT scanner table and must hold their breath for 8-10 seconds whilst the dye is injected and the images are taken. Please see supplementary material for details of the procedure and analysis.

Exposure assessment using myocardial contrast echocardiography to detect CMD

Myocardial contrast echocardiography (MCE) is a specialised ultrasound technique that assesses the ability of the myocardial microvasculature to dilate and increase its own blood flow, such as that during stress or exercise. The method involves intravenous administration of a microbubble contrast agent though a peripheral vein in the arm.

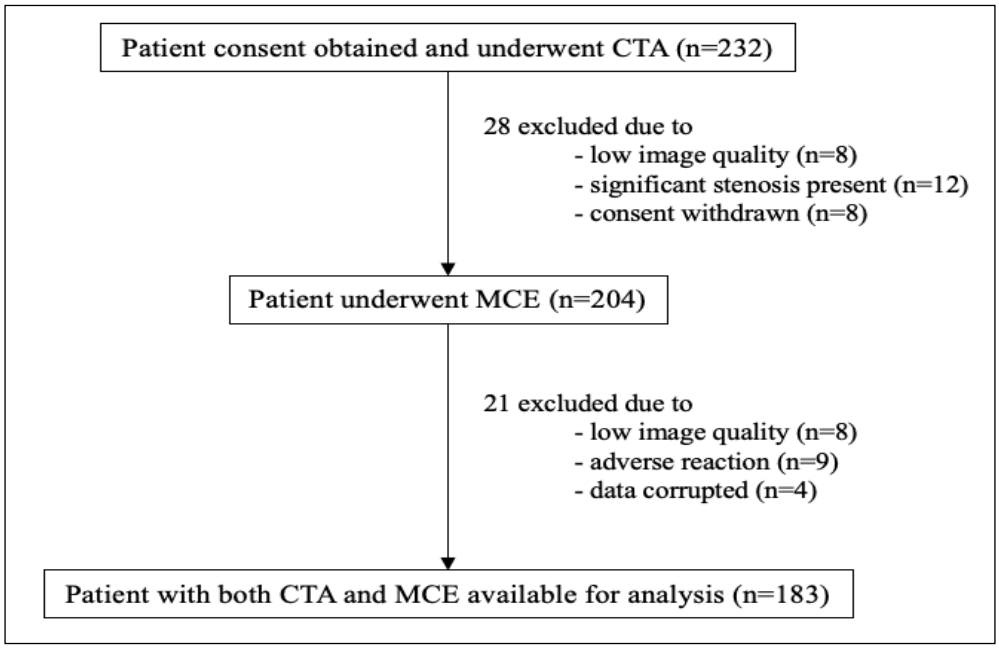
Ultrasound of the microbubbles in the heart allows measurement of myocardial blood flow (MBF) at rest. MBF measurement is then repeated once again following intravenous administration of a drug which increases myocardial blood flow (dipyridamole) - the stressor agent. The ratio of MBF during stress to the MBF at rest, is called the myocardial blood flow reserve (MBFR). The MBFR value is an assessment of microvascular function. Healthy hearts usually increase have a global MBFR of >2.0 (10). MCE allows the measurement of MBFR in different regions of the heart which when averaged gives the overall global MBFR (17). Global CMD is defined as being present if the MBFR reserve is <2.0 (10). To investigate MBFR in different regions, the heart was divided into two sections – that supplied by the left and right coronary arteries. The average MBFR, and presence of CMD in the left (CMD_L) and right coronary arteries (CMD_R) were calculated. For a more detailed explanation of the methods used, please see the supplementary material.

Statistical analysis

Continuous variables were summarised using means and 95% confidence intervals [CI]. Ordinal and dichotomous variables were summarised using proportions (percentages). Univariate logistic regression was used to quantify the association between a global CMD (MBFR cut-point of <2.0) and typical angina. Multivariate logistic regression was also performed with age, sex and diabetes entered into the model. The presence of diabetes was determined if the patient self-reported they had diabetes. To examine effect modification by sex, we analysed the CMD-angina relationship separately in men

and women, and used the likelihood ratio (LR) test to test for homogeneity. Effect sizes were reported as odds ratios with 95% confidence intervals (CI). The same analyses were repeated using regional MBFR derived from the left and right coronary artery territories. For sensitivity analyses, we repeated the analyses using lower MBFR cut-points (<1.8 and <1.6). All analyses were performed using STATA^{TM} version 12.0.

Figure 2. Flow diagram of participants included and excluded from the study with reasons for non-participation.



Results

The flow diagram of participants is shown in Figure 2. Out of 232 consented, 183 had images for both CTA and MCE analysis. Patients had a mean age of 59.8(58.4-61.2) years of whom 52% were male (Table 1). The left coronary system was dominant in 1%(2) and atherosclerotic plaque present in 62%(113) participants. Mean global MBFR (mean, 95% CI) for the whole patient cohort was 2.20(2.12-2.27). Of the total group, global CMD was present in 38%(70), global MBFR <1.8 in 22%(41), and global MBFR <1.6 in 11%(21). The mean MBFR in the left and right coronary artery territories was 2.27$\pm$1.88 and 2.18$\pm$1.41, respectively. Of the total group, 35%(64) had CMD_L and 40%(73) CMD_R.

Table 1. Characteristics of the study sample.

		Total number of patients (%) or mean value (95% CI)
Number of participants		183(100%)
Age (years)		59.8(58.4-61.2)
Male		96(52%)
BMI (Kg/m^2)		27.2(26.7-27.8)
Hypertension		71(39%)
Diabetes		19(10%)
Total cholesterol (mmol/l)		5.2(5.1-5.4)
Triglyceride (mmol/l)		1.6(1.4-1.8)
Family history of ischemic heart disease		91(50%)
Medications	ACE inhibitor	27(15%)
	B-blocker	48(26%)
	Calcium blocker	35(19%)
	Statin	66(36%)
	Aspirin	66(36%)
Smoker		19(10%)
Global MBFR		2.20(2.12-2.27)
Global CMD		70(38%)

Typical angina was present in 63 participants, a prevalence of 34% (95% CI: 28-42%) (Table 1). Uni- and multivariate regression analysis did not find a significant association between global CMD and typical angina symptoms either overall [aOR 1.65 (95% CI: 0.87-3.12), p=0.13] (Table 2), or when stratified according to gender: women [aOR 1.92, (95% CI:0.76-4.88), p=0.17], or in men [aOR 1.44, 95% CI: 0.59-3.52, p=0.42] (Table 3). RCA CMD was significantly associated with angina [aOR 3.68(1.92-7.04), p<0.001] overall (Table 2), and also when stratified according to sex: in both women [aOR

4.30(1.67-11.1) p=0.003)], and men [aOR 3.13(1.26-7.78)], p=0.014) (test for homogeneity, p= 0.67) (Table 3). LCA CMD was not associated with angina overall [1.57(95% CI 0.83-2.99), p=0.17), in women [aOR 1.26(95% CI 0.48-3.26), p=0.64] or men [aOR 1.84(95% CI 0.76-4.45), p=0.18] (tables 2 and 3).

Table 2. Univariate and multivariate logistic regression analysis whether the presence of coronary microvascular dysfunction (CMD) globally, or the presence of CMD in the right (RCA CMD) and left (LCA CMD) coronary artery territories, are associated with typical angina symptoms*. Unadjusted (OR) and adjusted odds ratios (aOR), 95% confidence intervals and p values, are given.

		Angina n(%)	OR	95%CI	P value	aOR	95%CI	P value
Global CMD	Yes	30(43%)	1.82	0.97-3.39	0.06	1.65	0.87-3.12	0.13
	No	33(29%)	-	-	-	-	-	-
RCA CMD	Yes	38(52%)	3.69	1.95-7.00	0.000	3.68	1.92-7.04	0.000
	No	25(23%)	-	-	-	-	-	-
LCA CMD	Yes	27(42%)	1.68	0.89-3.16	0.11	1.57	0.83-2.99	0.17
	No	36(30%)	-	-	-	-		-

*other explanatory variables in multivariate regression model: age, diabetes, sex. None were significantly associated with typical angina; for simplicity these are not given.

Table 3. Univariate and multivariate logistic regression* analysis stratified according to sex, showing whether the presence of coronary microvascular dysfunction (CMD) globally or in regions corresponding to right and left coronary artery territories (RCA CMD and LCA CMD), are associated with typical angina symptoms.

		Male (n=96)							Female (n=87)						
		Angina n (%)	OR	95%CI	P value	aOR	95%CI	P value	Angina n (%)	OR	95%CI	P value	aOR	95%CI	P value
Global CMD	Yes	16(43%)	1.74	0.74-4.08	0.206	1.44	0.59-3.52	0.42	14(42%)	1.92	0.77-4.77	0.162	1.92	0.76-4.88	0.169
	no	18(31%)	-	-	-	-	-	--	15(28%)	-	-	-	-	-	-
RCA CMD	Yes	20(51%)	3.23	1.35-7.72	0.008	3.13	1.26-7.78	0.014	18(53%)	4.30	1.67-11.1	0.003	4.30	1.67-11.1	0.003
	No	14(24%)	-	-	-	-	-	-	11(21%)	-	-	-	-	-	-
LCA CMD	Yes	17(46%)	2.1	0.89-4.95	0.09	1.84	0.76-4.45	0.175	10(37%)	1.27	0.49-3.29	0.623	1.26	0.48-3.26	0.639
	No	17(29%)	-	-	-	-	-	-	19(32%)	-	-	-	-	-	-

*other explanatory variables in multivariate regression model: age, diabetes, sex. None were significantly associated with typical angina; for simplicity these are not given.

In the sensitivity analysis, global MBFR at the lower cut points (<1.8 and <1.6) did not show any significant association with typical angina (Table 4). In the RCA territory but not the left, RCA MBFR < 1.8 was significantly associated with typical angina [aOR 2.51 (1.27-4.98), p=0.008] (Table 5). When stratifying according to sex, for females, RCA MBFR cut points of <1.8 and < 1.6 were both significantly associated with typical angina: aOR 5.17(95%CI: 1.90-14.1), p=0.001, and aOR 5.53(95% CI: 1.67-18.3), p=0.005, respectively (Table 6). In the RCA territory for males at the lower cut points, there was no association. In the left coronary territory there was no significant association between the LCA MBFR lower cut-points and typical angina, for either sex.

Table 4. Sensitivity analyses. Univariate and multivariate logistic regression* analysis assessing whether global MBFR reductions at different cut points of <1.8 and 1.6, are associated with typical angina symptoms*. Unadjusted (OR) and adjusted odds ratios (aOR), 95% confidence intervals and p values, are given.

		Angina	OR	95%CI	P value	aOR	95%CI	P value
Global MBFR<1.8	Yes	19(46)	1.92	0.95-3.91	0.06	1.71	0.83-3.55	0.145
	No	44(31)	-	-	-	-	-	-
Global MBFR <1.6	Yes	9(43)	1.50	0.60-3.78	0.39	1.24	0.48-3.23	0.654
	No	54(33)	-	-	-	-	-	-

*other explanatory variables in multivariate regression model: age, diabetes, sex. None were significantly associated with typical angina; for simplicity these are not given.

Table 5. Sensitivity analyses. Univariate and multivariate logistic regression* analysis assessing whether MBFR reductions at different cut points of <1.8 and 1.6 in the right (RCA) and left (LCA) coronary artery territories, are associated with typical angina symptoms. Unadjusted (OR) and adjusted odds ratios (aOR), 95% confidence intervals and p values, are given.

	Right coronary artery territory							
		Angina n(%)	OR	95%CI	P value	aOR	95%CI	P value
RCA MBFR <1.8	Yes	26(50%)	2.54	1.31-4.93	0.006	2.51	1.27-4.98	0.008
	No	37(28%)	-	-	-	-	-	-
RCA MBFR <1.6	Yes	17(46%)	1.85	0.89-3.85	0.10	1.69	0.79-3.61	0.18
	No	46(32%)	-	-	-	-	-	-

	Left coronary artery territory							
		Angina n(%)	OR	95%CI	P value	aOR	95%CI	P value
LCA MBFR <1.8	Yes	17(41%)	1.48	0.72-3.02	0.28	1.36	0.66-2.82	0.41
	No	46(32%)	-	-	-	-	-	-
LCA MBFR <1.6	Yes	9(35%)	1.01	0.42-2.42	0.98	0.90	0.37-2.20	0.8
	No	54(34%)	-	-	-	-	-	-

*other explanatory variables in multivariate regression model: age, diabetes, sex. None were significantly associated with typical angina; for simplicity these are not given.

***Table 6. Sensitivity analyses. Univariate and multivariate logistic regression* analysis stratified according to sex, assessing whether MBFR reductions at different cut points of <1.8 and 1.6, in the left (LCA) and right coronary artery (RCA) territories are associated with typical angina symptoms. Unadjusted and adjusted odds ratios, 95% confidence intervals and p values are given** *

		Male (n=96)							Female (n=87)						
		Angina n (%)	OR	95%CI	P value	aOR	95%CI	P value	Angina n (%)	OR	95%CI	P value	aOR	95%CI	P value
Global MBFR <1.8	Yes	11(46%)	1.80	0.70-4.63	0.221	1.56	0.59-4.14	0.373	8(47%)	2.07	0.70-6.11	0.186	2.06	0.67-6.30	0.206
	no	23(32%)	-	-	-	-	-	-	21(30%)	-	-	-	-	-	-
Global MBFR <1.6	Yes	6(46%)	1.68	0.52-5.49	0.387	1.26	0.36-4.34	0.717	3(38%)	1.22	0.27-5.51	0.793	1.16	0.25-5.40	0.846
	No	28(34%)	-	-	-	-	-	-	26(32%)	-	-	-	-	-	-
RCA MBFR <1.8	Yes	11(41%)	1.38	0.55-3.44	0.496	1.21	0.45-3.24	0.71	15(60%)	5.14	1.89-13.9	0.001	5.17	1.90-14.1	0.001
	No	23(33%)	-	-	-	-	-	-	14(23%)	-	-	-	-	-	-
RCA MBFR <1.6	Yes	7(32%)	0.81	0.29-2.24	0.688	0.55	0.17-1.76	0.311	10(67%)	5.58	1.69-18.4	0.005	5.53	1.67-18.3	0.005
	No	27(36%)	-	-	-	-	-	-	19(26%)	-	-	-	-	-	-
LCA MBFR <1.8	Yes	11(44%)	1.64	0.64-4.17	0.299	1.52	0.58-3.97	0.395	6(37%)	1.25	0.41-3.87	0.70	1.20	0.38-3.81	0.760
	No	23(32%)	-	-	-	-	-	-	23(32%)	-	-	-	-	-	-
LCA MBFR <1.6	Yes	8(44%)	1.60	0.56-4.54	0.377	1.32	0.45-3.89	0.61	1(13%)	0.26	0.03-2.22	0.219	0.24	0.27-2.08	0.20
	No	26(33%)	-	-	-	-	-	-	28(35%)	-	-	-	-	-	-

*other explanatory variables in multivariate regression model: age, diabetes, sex. None were significantly associated with typical angina; for simplicity these are not given

Discussion

This study demonstrated that a third of patients referred to clinics with chest pain and normal coronary arteries have CMD. Global CMD was not associated with typical angina but the presence of CMD in the right coronary artery territory was associated with angina in both males and females. The strength of this association was similar in men and women.

The prevalence of CMD found in our study is similar to that found in other studies which ranges from 25% to 60% depending on the patient group selected (clinic, emergency department, angiography) and the methods used to assess MBFR. The mechanism by which CMD may cause angina is not fully understood. Traditional thinking suggests that for CMD, like obstructive CAD, the symptoms of angina occur as a result of an oxygen supply/demand imbalance (5, 6). Myocardial ischemia leads to local build-up of metabolites such as adenosine, bradykinin, lactate and potassium (24). Local chemoreceptors transmit afferent impulses via sensory nerve endings which coalesce with the sympathetic and vagal components, and then enter the dorsal root ganglia. Passing into the medulla, midbrain, thalamus and pre-frontal cortex, complex interactions between these different regions occur which modulate the perception of pain (25). Factors known to influence the handling of chest pain include mood, anxiety, anticipation and altered pain thresholds (5).

The original concept that CMD was the cause of angina symptoms in patients with unobstructed coronary arteries was derived from patients with Cardiac Syndrome X. This

syndrome was characterised by patients with 1) anginal chest pain triggered by effort, 2) ST segment depression on exercise ECG testing or evidence of myocardial ischemia on functional testing, and 3) normal, or near normal, coronary arteries on coronary angiography (26). When these small and highly selective groups of patients were studied and compared with asymptomatic age- and sex-matched healthy controls, it was noted that a large proportion of the Syndrome X patients had CMD. It was therefore proposed that CMD might be the cause of chest pain. However, CMD is has been shown to be common in the general population, with one study demonstrating 25% of asymptomatic women having CMD (15). This is because CMD is caused by other factors such as smoking, hypertension and hypercholesterolemia, many of which are risk factors for cardiovascular disease (13).]

Subsequent studies have sought to demonstrate a greater prevalence of CMD in larger unselected groups of patients presenting with chest pain and unobstructed coronary arteries, but the majority have failed to find a link (8, 14). One study using PET looked at the prevalence of CMD in 405 men and 813 women with typical or atypical angina, without obstructive CAD, and found no difference in global CFR between the two groups (8). Another larger study investigated 963 women without obstructive CAD, and used transthoracic Doppler in the left anterior descending coronary artery to measure CMD, but did not find any association between chest pain typicality and the presence of CMD (14). A more recent study by Bove et al investigating CMD in 1684 women also using transthoracic Doppler, found a greater prevalence of CMD in patients with angina

compared with asymptomatic women, but this association disappeared when other risk factors such as age, smoking and hypertension were included in the model (15).

Consistent with these findings, our study also showed that the presence of CMD when measured as an average of all regions of the left ventricle, did not show a significant association with typical angina symptoms. Furthermore, the presence of CMD in the left coronary artery territory in our study was not associated with typical angina, and is consistent with those studies that measured CMD using Doppler of the left coronary artery.

The reason why the presence of CMD in right coronary artery region is associated with typical anginal chest pain, is not clear. The central autonomic nervous system plays an important role in the regulation of microvascular function (27). For example, in patients with microvascular angina, it has been shown that psychosocial stress causes the central autonomic nervous system network to be dysfunctional and lead to CMD. Anatomically, the right coronary artery territory of the left ventricle is predominantly supplied by parasympathetic fibres, and therefore an abnormality in this system may explain the occurrence of CMD and typical angina in this group of patients (25).

Strengths and limitations

This study recruited consecutive male and female patients attending clinics for the investigation of chest pain. The reasons for referral depend on the individual judgements of the clinician and are therefore subject to referral bias. Furthermore, the number of patients who were approached in clinics yet declined to participate is not

known and is subject to selection bias. Chest pain history assessment is subjective and therefore to reduce this effect this we used the well-validated Rose Angina questionnaire. This was a single centre study and therefore may suffer from the inherent biases associated with this and limits the generalisability of the results. Although all patients underwent CT coronary angiography to rule out the presence of obstructive coronary artery disease, 17% were unable to provide MCE for analysis for reasons such as consent withdrawal, low image quality and adverse reaction which may cause exclusion bias. Although MCE is a well validated technique for the measurement of myocardial microvascular function and has been used in the measurement of global and segmental MBFR, confirmation of these findings by other groups using different techniques such as PET is needed.

Conclusion

This study demonstrated that a third of patients referred to clinics with chest pain and unobstructed coronary arteries have CMD. Global CMD was not associated with typical angina but the presence of CMD in the right coronary artery territory was associated with angina in both males and females. The strength of this association was similar in men and women.

Supplementary material

Method for CT angiography imaging and analysis

This was performed using a 64-channel CT scanner (GE Lightspeed VCT, GE Medical Systems). Reconstructed CTA images were analyzed on a dedicated 3-dimensional workstation (CardIQ Xpress, GE Medical Systems) with curved multiplanar reformation and short-axis cross-sectional viewing techniques. Briefly, helical scan data was obtained using prospective ECG triggering. The contrast-enhanced scan injected 80mls contrast at 6 ml/s, followed by saline flush, during a single breath hold. CTA scan parameters: collimator 20mm, slice thickness 0.625mm; gantry rotation 350ms; helical acquisition using a pitch of 0.16; tube current 455-515 mA with ECG tube current modulation; tube voltage range 100-140kV; rotation time, 350ms. The mean radiation dose per patient was 3.3 mSv. Analysis was performed blind to patient demographic and MCE data. Plaque morphology with CT density of >150 Hounsfield units was considered to represent calcification, and <150 Hounsfield units to represent non-calcific plaque (28). Percentage diameter stenosis was calculated by dividing the minimal lumen diameter at each plaque by the nearest proximal normal artery diameter.

Method for myocardial contrast echocardiography and analysis

Myocardial contrast echocardiography is an established technique used in the non-invasive quantification of myocardial blood flow reserve (MBFR) and is used to assess microvascular function (17). In the absence of flow-limiting CAD, an MBFR <2.0 is indicative of underlying CMD (10). As this method assesses myocardial blood flow

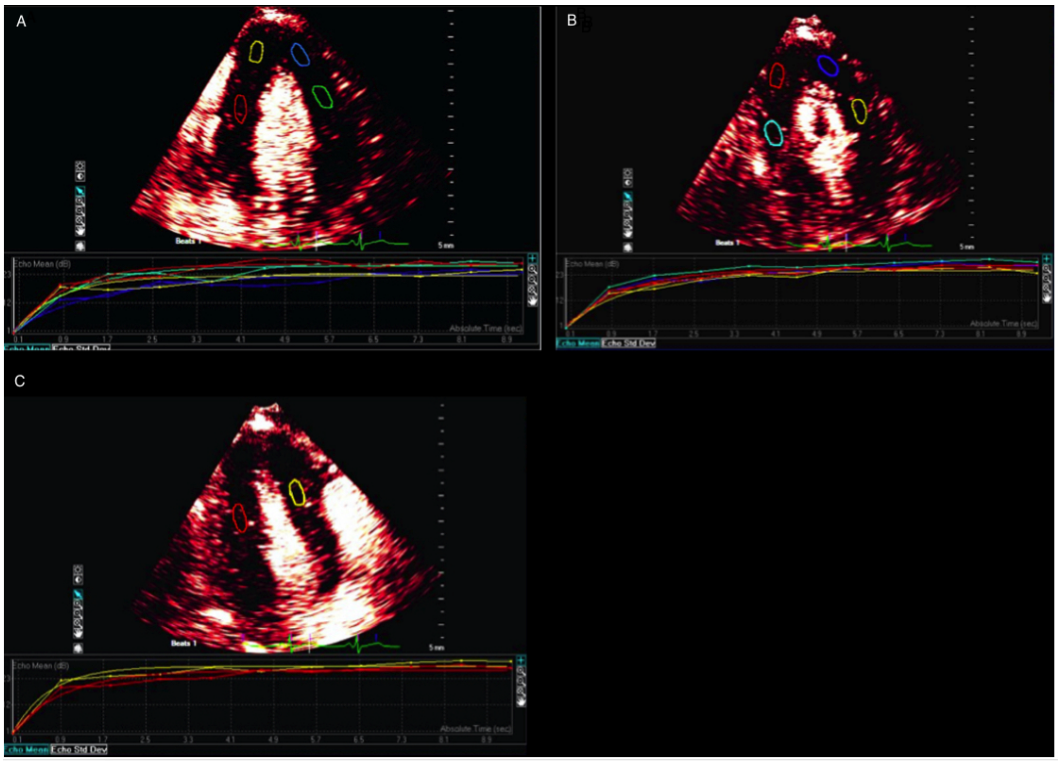
through direct visualisation of the different myocardial segments, microvascular function can be assessed at a both regional and whole-of-myocardium (global) level.

Patients underwent MCE study having avoided all caffeine-containing products, beta-blockers, nitrates and calcium antagonists in the previous 24 hours. MCE was performed using a commercial ultrasound machine iE33 (Philips Medical Systems) and SonoVue (Bracco Research SA) as the contrast agent given as constant infusion. Real-time images were recorded within 3-4 minutes in the apical 4-, 2- and 3-chamber views with low-power settings at a mechanical index of 0.1. The focus was set at the mitral valve level. SonoVue was initially started at 60 mL/hour through a peripheral vein cannula with the VueJect infusion syringe pump (Bracco Research, SA), which gently rotates and maintains the contrast agent in a suspension. Thereafter, the rate was set between 48 and 60 mL/hour to maximize image quality with minimal attenuation. Once optimized, the machine settings were held constant throughout each participant study. Flash-impulse imaging at a high mechanical index (1.0) was performed to achieve complete myocardial bubble destruction, after which 10 end-systolic frames were recorded digitally in each apical view. After the resting images were acquired, dipyridamole was infused at 0.56 mg/kg over a 4-minute period. After an interval of 2 minutes, post-stress images were recorded within 3 to 4 minutes. This entire sequence took 14 minutes.

Quantitative MCE analysis was performed offline using QLab V7.0 (Philips Medical Systems) and blind to patient demographic and CTA data.[19] Quantitative assessment of myocardial perfusion was performed for 10 consecutive end-systolic frames after microbubble destruction. A region of interest was placed over the thickness of the

myocardium. Plots of peak myocardial contrast intensity (linearly related to myocardial blood volume A cm^3) versus pulsing intervals (representing time) were automatically constructed to fit the monoexponential growth function : $y=A\ (1 - e^{-\beta t})$ where β is the instantaneous initial slope of the resulting curve and represents myocardial blood velocity (sec^{-1}) and the product of A and β yields a reliable measure of MBF ($cm^3.sec^{-1}$).[20] MBFR is the ratio of post-dipyridamole (stress) MBF to baseline MBF, dividing the stress MBF by the baseline MBF for the same segment. A 16-segment model was used excluding the basal segments in view of contrast attenuation, and analyzing the 10 remaining mid- and apical cardiac segments (Figure 1A below).

***Figure 1A Method used for quantitative analysis of myocardial segments: Apical 4 chamber (A), (Apical 2 chamber (B), Apical 3 chamber (C). Coloured software-constructed replenishment curves below each apical view correspond to each region of interest manually drawn*.**



A segment was excluded if there was artefact, inadequate microbubble destruction, attenuation or a wide variation in contrast intensity. Segmental MBFR was calculated by dividing peak MBF with resting MBF of the same segment. Whole-of-heart or 'global' MBFR ($MBFR_G$) was the average MBFR of all myocardial segments. To estimate regional MBFR, the left ventricle was divided into those segments supplied by the left ($_L$) and the right ($_R$) coronary arteries, adjusting the segments included according to coronary artery dominance. $MBFR_L$ and $MBFR_R$ was calculated as the average MBFR of the regional segments involved. $MBFR_L$ consisted of a minimum of 4 segments and $MBFR_R$ a minimum of 2 segments.

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CHAPTER 6

TEACHING AND EVIDENCE OF ADDITIONAL REQUIREMENTS

Table of Contents

List of Figures

Literature search and synthesis of relevant information

All four chapters required review of the literature and synthesis of relevant information relevant to each topic. Specifically, chapters 3 and 4 are centred around cardiovascular disease prevention and required extensive review, acquistion of new and additonal knowledge. Evidence of this can be gauged from the introductions and discussions in each of these chapters. Furthermore, a strong knowledge of the literature was required to present to a wide range of audiences, participate in a workshop regarding develpement of the new national cardioavscular disease prevention guidelines, and publish two peer reviewed articles during my MAE period. Chapter 5 relates to coronary microvascular dysfunction and this required me to update my knowledge of the latest literature.

Report on a project to a non-scientific audience such as the community or other stakeholder, as a press release, or in the form of a ministerial brief.

The ATHENA COVID-19 Study required the development of a website which contained information that could be available to inform both potential partcipants and the public about the project, as well as GPs. I wrote all of the text which went onto the website which included the overview and objectives of the study, participant/patient information forms, information for general practices, frequently asked questions, and reasons why patients should participate. I also wrote all of the scripts which the call centre used when contacting patients. The site can be found on the Queensland Health web site under the ATHENA COVID-19 Study. A screenshot of the landing page is shown in Figure 1, along with the text I wrote for the public and partcipants to view (figures 2-5). Relevant additional material is also found in the Appendix (figures 2A and 3A).

Figure 1. Screenshot of landing page for the ATHENA COVID-19 Study

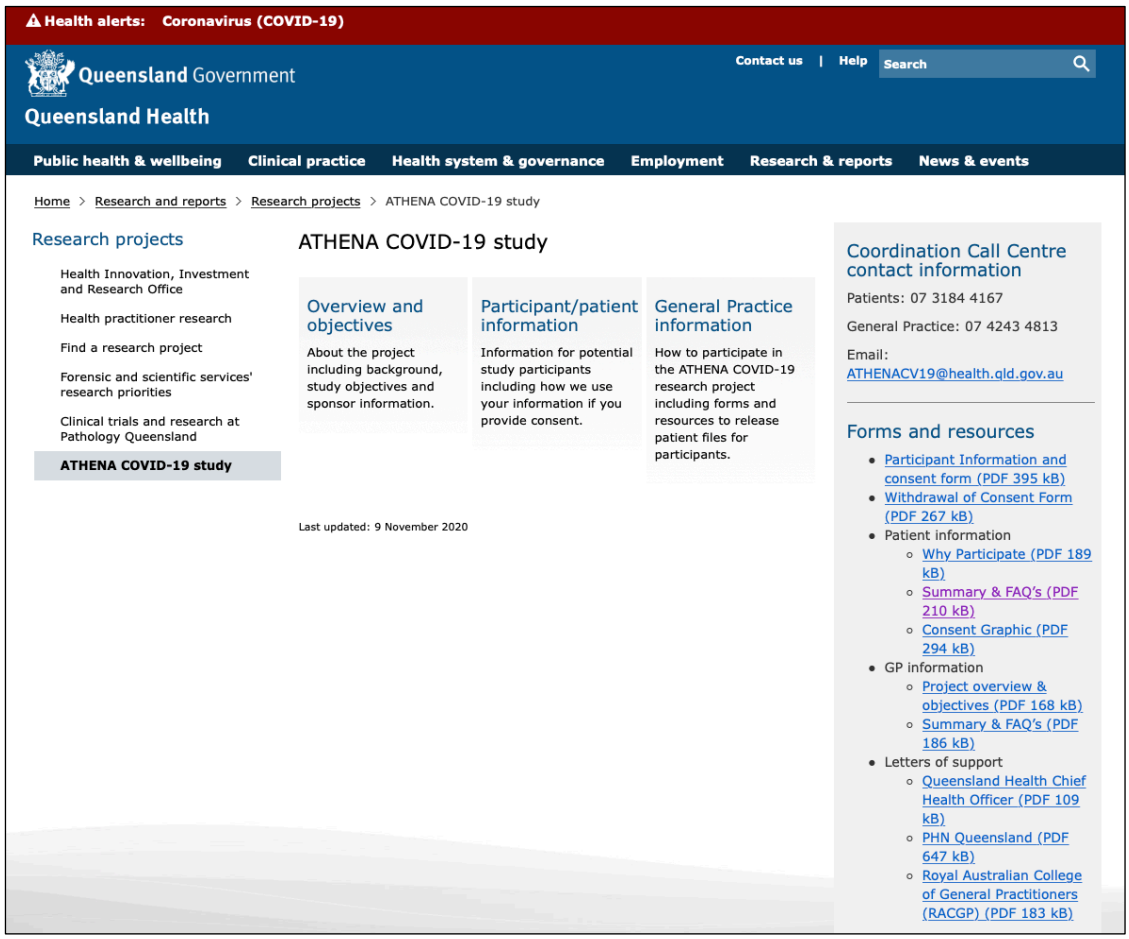


Figure 2. Web pages: overview and objectives of the ATHENA COVID-19 Study information for the public

Overview and objectives

On this page:

- Background
- Objectives
- Research team

This research study aims to describe the health outcomes of **people diagnosed with COVID-19** in Queensland, over time and in relation to patient characteristics, by combining COVID-19 notification, hospital, general practice and death registry data.

General practice patient health information, in comparison to hospital data, contains additional, more detailed and up-to-date information on patient characteristics, including health conditions and medications at the time of infection.

We will be contacting patients who have or have had COVID-19 and will be inviting them to participate by giving their individual consent.

Background

The novel coronavirus disease, named COVID-19 on 11 February 2020, is caused by SARS-CoV-2 virus.

The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. While the number of confirmed cases worldwide and in Australia is reported daily, detailed data on the outcomes of people who test positive for SARS-CoV-2, and predictors of outcomes, are still scarce.

Outcomes are likely to vary with context, including according to extensiveness of surveillance and testing, health systems functioning and population characteristics.

Evidence to date has come primarily from overseas countries that are further along in the pandemic than Australia.

Knowledge gaps in relation to COVID-19

There is limited information to date describing patient characteristics associated with outcomes, particularly in respect to the Australian population.

There is substantial variation by age, with younger people generally experiencing milder forms of disease, with a greater proportion of those with severe disease or death being older.

Importantly, these data to date have only been based on **hospitalised patients**, and do not include all patients who have been diagnosed with COVID-19 in the community.

Furthermore, **they do not include Australian data**. Australian-specific and state-specific data are **essential** as we continue through the epidemic as outcomes are dependent on a number of region-specific factors including population profile, health system factors and the public health actions taken by individuals and Government.

Study Objectives

The main objectives of the ATHENA COVID-19 STUDY are:

1. To quantify hospital-based outcomes and deaths, including in relation to sociodemographic characteristics and comorbidities as ascertained from hospital AND general practice data.
2. To estimate the strength of association between these outcomes and sociodemographic and health characteristics.

Study Sponsor

The Health Innovation, Investment and Research Office (HIIRO) of Queensland Health is responsible for consultation, development and review of State-wide research ethics and research governance policies.

HIIRO provides a central portal of contact for Researchers, HHS Human Research Ethics Committee Chairs and Members, Coordinators, Research Governance Offices/rs and study sponsors seeking advice and direction on ethical and governance issues associated with the conduct of research in Queensland Health.

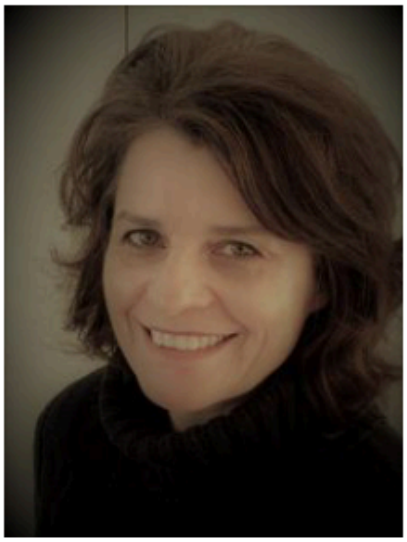
Meet the team

Professor Kim Greaves (BSc, MD, FACC, FRCP) Principal Investigator & Project Lead

Professor Greaves is the Director of Cardiac Research and a Senior Staff Specialist in Cardiology at the Sunshine Coast University Hospital, Queensland. He holds a Fellowship of the Royal College of Physicians (FRCP –UK), Fellowship of the Royal Australian College of Physicians (FRACP), and completed a Doctor of Medicine in 2007.

Kim has extensive experience and publications in medical research and holds academic appointments as Professor and Associate Professor at the Griffith University, the Australian National University, Queensland University of Technology, University of Sunshine Coast, and the University of Queensland. Professor Greaves is currently focusing on health information sharing for health service planning, delivery and research, and areas of implementation science applicable to cardiovascular disease prevention.

Associate Professor Rosemary Korda (BAppSc, MAppSc, GradDipPopHlth, PhD)
Principal Investigator and team lead for ANU



Data Analyses Team – Australian National University: National Centre for Epidemiology and Population Health, Research School of Population Health

Rosemary Korda is an Associate Professor at the National Centre for Epidemiology and Population Health, working in chronic disease epidemiology and health services research. She has extensive experience in the analysis of large-scale complex data, including longitudinal survey data and linked administrative health data.

Current research interests include:

- innovation in use of linked data
- inequalities in cardiovascular disease and healthcare
- unwarranted variation in care; and
- health risks of environmental exposures, including asbestos insulation and per- and poly-fluoroalkyl substances (PFAS).

In addition to her research, she has a major role in curriculum development and teaching in postgraduate population health courses at the ANU and in supervising higher degree research students. She is currently serving as an Expert Member on the Australian Government's Prostheses List Advisory Committee (PLAC).

Dr Zoltan Bourne (FRACGP, BMed, BSc)
ATHENA COVID-19 Coordination Centre, Team Lead

Dr Zoltan Bourne is the Director and owner, for the past 13 years, of Medicine on Maple - a General Practice located in Maleny on the hinterland of the Sunshine Coast. He has been a Supervisor to General Practice Registrars for both RACGP and ACRRM and a Senior Lecturer for the Griffith University School of Medicine.

With a strong commitment to health system reform, he was the inaugural General Practice Liaison Officer for the Medicare Local and PHN where he strongly advocated for the introduction of HealthPathways and the Queensland Health General Practice Smart Referral.

More recently, Zoltan has worked with Prof Kim Greaves on the General Practice Data Linkage 'proof of concept study' which successfully progressed to 'The ATHENA study' and now 'The ATHENA COVID-19 study. Dr Bourne contributes expert advice to the project and will lead the ATHENA COVID-19 Coordination centre team.

Figure 3. Web page: Simple diagram to explain concept of the ATHENA COVID-19 Study for the public

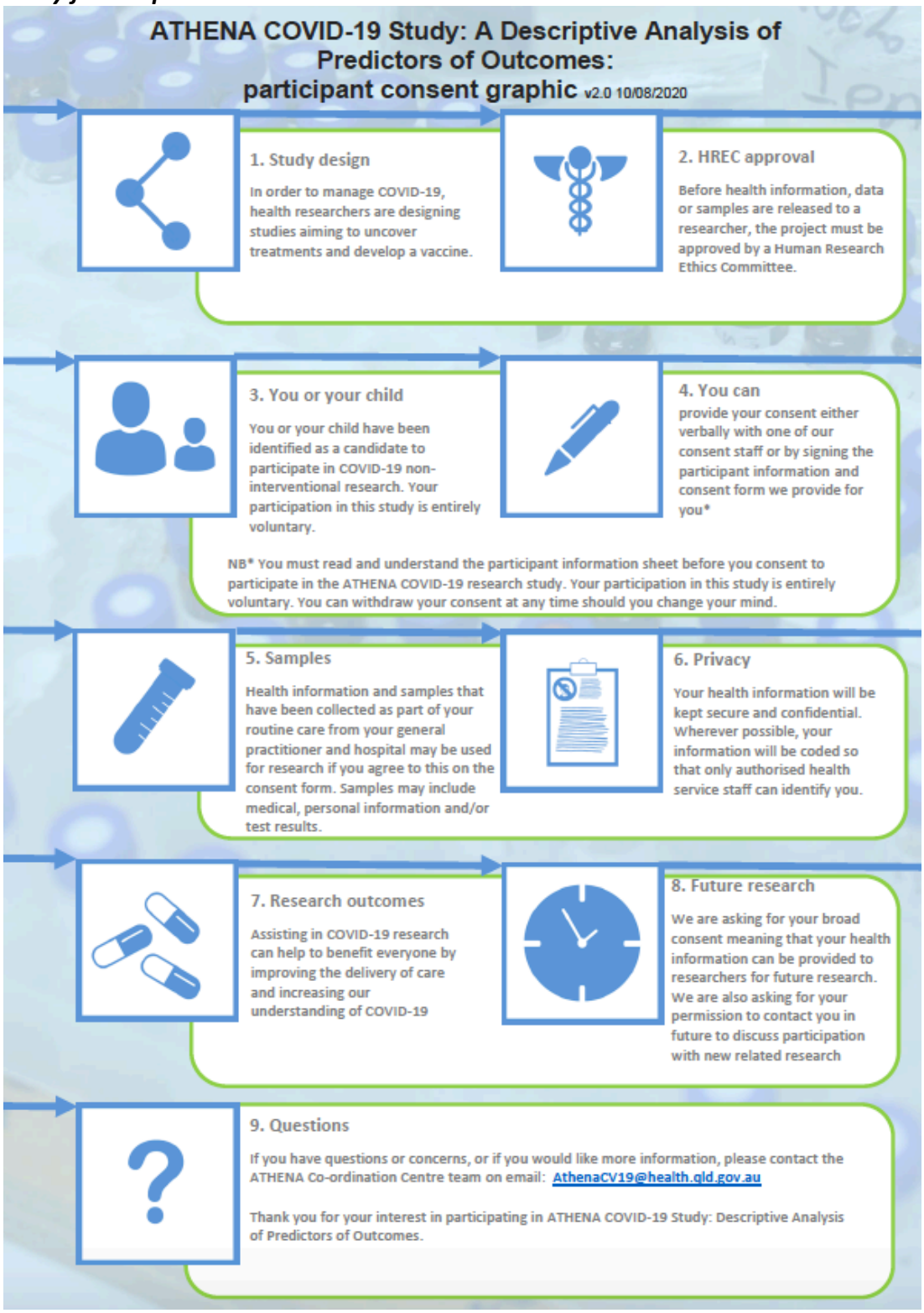


Figure 4. Web page: participation/patient information summary of study for ATHENA COVID-19

Participant/patient information

Summary of the study

This research study undertaken by Queensland Health and partners aims to answer vital questions about which medical conditions, medicines and other health characteristics are more likely to make patients infected with COVID-19 develop mild, moderate, or severe forms of the disease.

All of our evidence to date has come primarily from overseas countries who were ahead of us in the pandemic, but not Australia. **It is essential that we obtain local data as patient outcomes may be very different in Australia.**

We can do this by obtaining copies of all consented patients' health records who had COVID-19 in Queensland and combining them together for research analyses. By health records we mean those held in hospitals and general practices.

In order to access to these records, we need patient consent. This means we will be contacting all patients who had COVID-19 and inviting them to participate in the study. By giving consent, this will allow us to contact each patient's general practice and ask their GP to securely transfer a copy of that patient's health record to Queensland Health where it can be combined with their other health information.

The study has registered Human Ethics Committee approval and is compliant with all privacy legislation.

- This study requires patient consent. Contact will be made with patients in Queensland who have, or have had, infection with COVID-19.
- Patients will be sent an information pack containing information about the study.
- Patients will be contacted by phone to discuss the study and then invited to provide consent for Queensland Health to obtain a copy of the participants' identifiable health information held within their general practice, to link and store it with their health information in Queensland Health, and to use it for unspecified but ethically approved research related to COVID-19.
- Patients will also be invited to give consent for re-contact by the project team to discuss participation in future unspecified but ethically-approved COVID-19-related research. This establishes a basis for additional important research that may require biospecimens, which are likely to play an important role in determining patient outcomes.
- Patient health information provided by general practices will be securely transferred to Queensland Health in an encrypted format via a secure file transfer. The health information will contain patient identifiers as this is required to perform linkage with the health information contained within Queensland Health. The personal information is for linking purposes only and *will not* be made available to researchers analysing the data. All data provided to the researchers for analysis will be de-identified.
- For further information please contact the ATHENA COVID-19 Coordination Centre on: 07 3184 4167 or email: ATHENACV19@health.qld.gov.au.

Figure 5: Web page: reasons for the public/participants to support the ATHENA COVID-19 Study

Queensland Health

ATHENA COVID-19 Study

Principal Investigator: Professor Kim Greaves

BSc, MBBS, MD, FRCP (UK), FRACP

The **A**ustralians **T**ogether **HE**alth I**N**iti**A**tive

This study has the support of the Royal Australian College of General Practitioners (RACGP), all seven Primary Health Networks in Queensland and Queensland Health. The study is funded by the Health Innovation Investment and Research Office, Queensland Health.

Summary of the study

This research study undertaken by Queensland Health and partners aims to answer vital questions about which medical conditions, medicines and other health characteristics are more likely to make patients infected with COVID-19 develop mild, moderate, or severe forms of the disease.

All our evidence to date has come primarily from overseas countries who were ahead of us in the pandemic, but not Australia. It is therefore essential that we obtain local data as patient outcomes may be very different in Australia.

We can do this by obtaining copies of all patients' health records who had COVID-19 in Queensland and combining them together for research analyses. By health records we mean those held in hospitals and general practices.

In order to achieve access to these records, we need each patient's consent. This means we will be contacting all patients who had COVID-19 and inviting them to participate in the study. By giving consent, this will allow us to contact each patient's General Practice (GP) and asking their GP to securely transfer a copy of that patient's health record/information into Queensland Health where it can be linked with any of their other health information within the hospital.

All the health information provided to researchers outside of Queensland Health is de-identified. De-identification means removing identifying information from the data and samples i.e. you will be known to these researchers by a code and not by your name.

The combined de-identified health information will then be analysed by experienced researchers.

The study has registered Human Ethics Committee approval and is compliant with all privacy legislation.

ACV-19 Patient Information and FAQs V 2.1 20/10/2020 ATHENA is a Queensland Government initiative, supported by:

Australian National University

phn CENTRAL QUEENSLAND, WIDE BAY, SUNSHINE COAST

Queensland Government

Participants – Why Support the Queensland Health ATHENA COVID-19 Study?

1. The study will answer vital questions about which medical conditions, medicines and other health characteristics make you more likely to develop mild, moderate, or severe COVID-19 in our population.
2. The health information within general practices holds key information to better understand how COVID-19 impacts our population. Currently they remain isolated within your general practice. Sharing them with any health records you may have within Queensland Health would provide an invaluable resource to help health researchers further understand COVID-19. We need your permission to ask your GP clinic to send Queensland Health your health information and to allow researchers to analyse the combined health information.
3. Any health information provided to health researchers is de-identified. De-identification means removing identifying information from the data and samples i.e. you will be known to these researchers by a code and not by your name
4. The study has the support of Royal Australian College of General Practitioners, the Queensland Health Chief Health Officer and all 7 Queensland Primary Health Networks.
5. The study has registered Human Ethics Committee approval and is compliant with all privacy legislation.

Prepare an advanced draft of a paper for publication in a national or international peer-reviewed journal

My thesis resulted in the publication of three manuscripts in peer-reviewed journals. The contents of Chapter 2 *('The ATHENA COVID-19 Study - Part 1: Cohort profile and first findings for people diagnosed with COVID-19 in Queensland 1 January to 31 December 2020. Part 2: linkage of general practitioner data and consent-to-recontact'*) have been accepted for publication in in Communicable Diseases Intelligence. Chapter 4 *('A Cross-Sectional Survey Describing General Practitioners' Absolute Cardiovascular Disease Risk Assessment Practices and their Relationship to Knowledge, Attitudes and Beliefs about Cardiovascular Disease Risk in Queensland, Australia')* was published in the BMJ Open on August 13th 2020. Influenced by, and related to this work, I completed another project on CVD prevention during my MAE period, which was also published in the BMJ Open on February 8th 2021 *('Absolute*

cardiovascular disease risk score and pharmacotherapy at the time of admission in patients presenting with acute coronary syndrome due to coronary artery disease in a single Australian tertiary centre: a cross-sectional study'). A copy of manuscript is attached in the Appendix Figure 5A. Chapter 2 on CVD surveillance and treatment is prepared for publication and will be submitted. Chapter 5 on chest pain and coronary microvascular dysfunction is also in publication format too.

Presentation at a national or international conference

I gave two presentations on CVD prevention at the Australian Practice Nurse Association national conference held in Brisbane in 2018, and also at the national Primary Health Network conference in Sydney in 2019. In both of these presentations, I talked about cardiovascular disease prevention and surveillance and included some of the results of my MAE projects. I have attached the presentation to at the Primary Health Network conference in the Appendix (Figure 6A).

Evidence of teaching experience

Combined teaching for first year MAE students

Our group of three (Freya Hogarth, Stephanie Main, myself) undertook an introductory teaching session to the first year MAE cohort over a 40 minute period on how to use REDCap (Research Electronic Data Capture). The learning objectives included an overview, why you would use REDCap, how to navigate the interface, and how you would create a basic survey for data collection. We then had two breakout groups whereby we showed students in a walk-through demonstration, how to create a survey. The feedback evaluation scores on our teaching session indicated it was well received. The evaluation scores and slides used, are attached in the Appendix (figures 7A and 8A).

Other teaching

I regularly taught medical students, nurses, junior doctors, general practitioners, PHN staff and departmental colleagues, about cardiovascular disease prevention, data linkage and other work from my MAE thesis. This occured informally on weekly ward rounds, formally at departmental meetings, and at health service organised events.

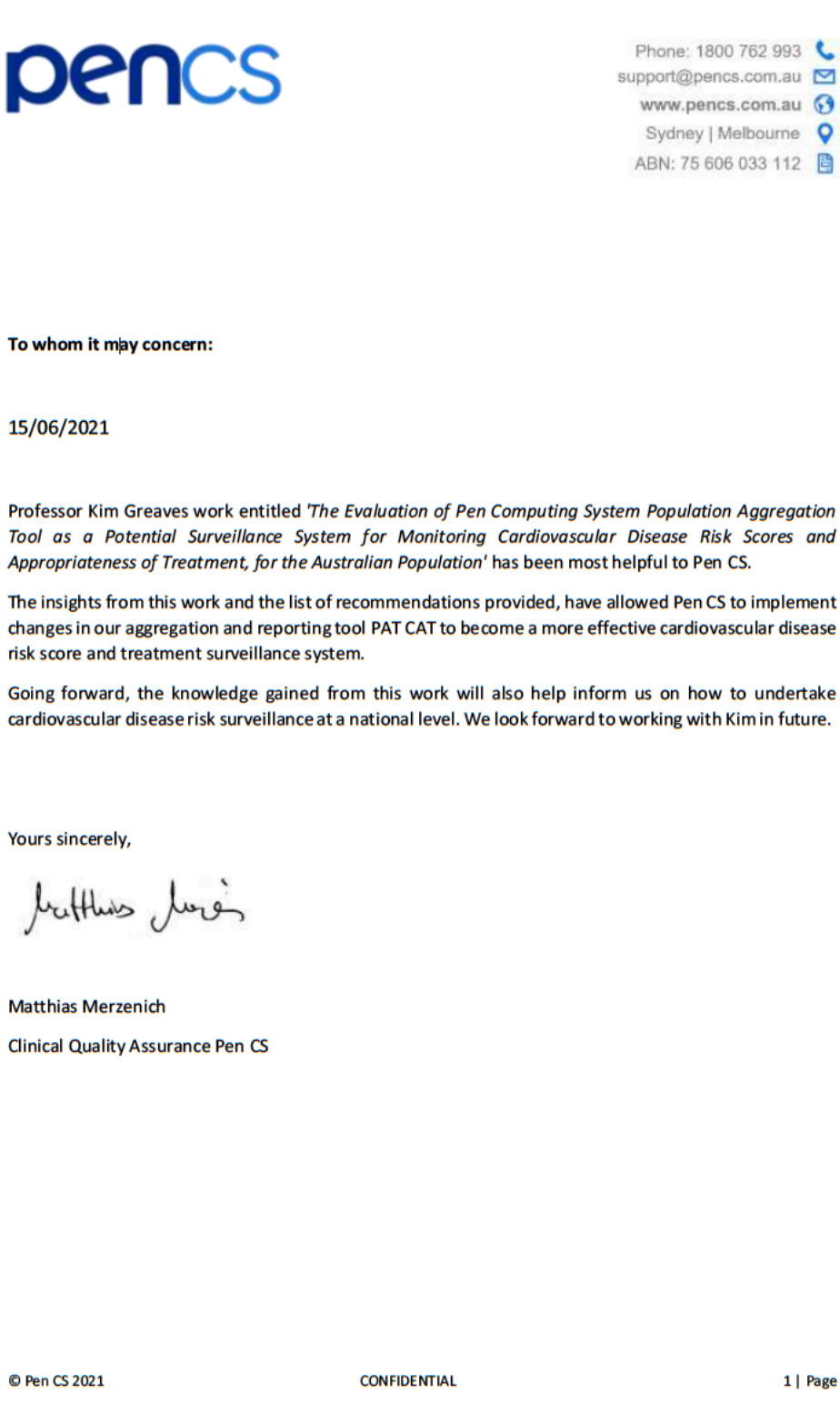
Lessons from the field

I gave this presentation to my group on June 21st 2021. This described the concept of the ATHENA COVID-19 Study and the principles of data linkage including the Separation Principle. I also described the obstacles we enountered setting up the study, how we overcame and worked around them. The slides are shown in the Appendix, Figure 8A.

APPENDIX

List of figures

Figure 1A. Letter from Pen CS indicating they are implementing the list recommendations following evalaution of their cardiovascular disease risk surveillance system PAT CAT.



pencs

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support@pencs.com.au
www.pencs.com.au
Sydney | Melbourne
ABN: 75 606 033 112

To whom it may concern:

15/06/2021

Professor Kim Greaves work entitled *'The Evaluation of Pen Computing System Population Aggregation Tool as a Potential Surveillance System for Monitoring Cardiovascular Disease Risk Scores and Appropriateness of Treatment, for the Australian Population'* has been most helpful to Pen CS.

The insights from this work and the list of recommendations provided, have allowed Pen CS to implement changes in our aggregation and reporting tool PAT CAT to become a more effective cardiovascular disease risk score and treatment surveillance system.

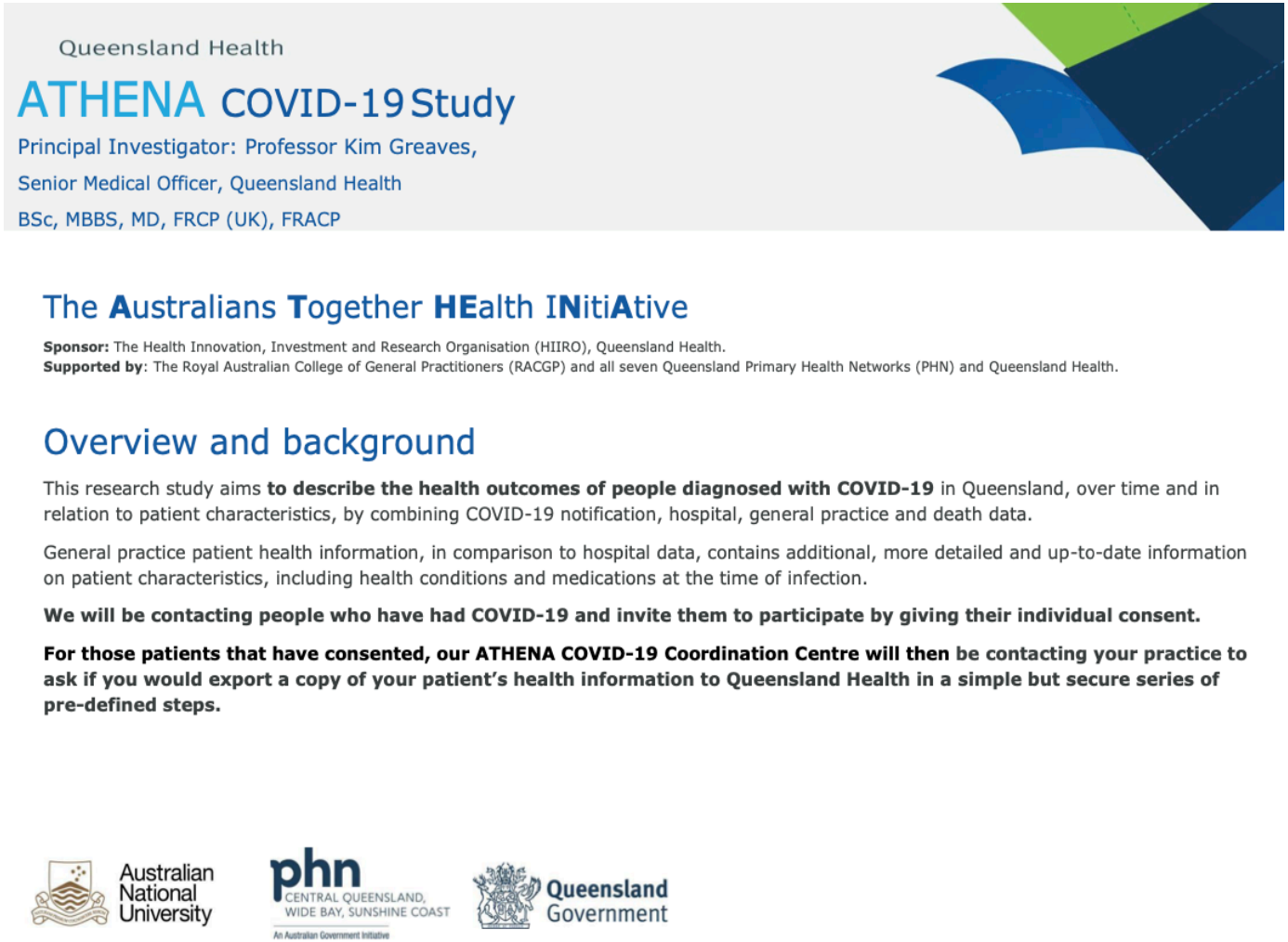
Going forward, the knowledge gained from this work will also help inform us on how to undertake cardiovascular disease risk surveillance at a national level. We look forward to working with Kim in future.

Yours sincerely,

Matthias Merzenich

Clinical Quality Assurance Pen CS

Figure 2A. Web page for GPs: screenshots of the different Queensland Health web pages for the ATHENA COVID-19 Study.



Queensland Health

ATHENA COVID-19 Study

Principal Investigator: Professor Kim Greaves,
Senior Medical Officer, Queensland Health
BSc, MBBS, MD, FRCP (UK), FRACP

The **A**ustralians **T**ogether **HE**alth I**N**iti**A**tive

Sponsor: The Health Innovation, Investment and Research Organisation (HIIRO), Queensland Health.
Supported by: The Royal Australian College of General Practitioners (RACGP) and all seven Queensland Primary Health Networks (PHN) and Queensland Health.

Overview and background

This research study aims **to describe the health outcomes of people diagnosed with COVID-19** in Queensland, over time and in relation to patient characteristics, by combining COVID-19 notification, hospital, general practice and death data.

General practice patient health information, in comparison to hospital data, contains additional, more detailed and up-to-date information on patient characteristics, including health conditions and medications at the time of infection.

We will be contacting people who have had COVID-19 and invite them to participate by giving their individual consent.

For those patients that have consented, our ATHENA COVID-19 Coordination Centre will then be contacting your practice to ask if you would export a copy of your patient's health information to Queensland Health in a simple but secure series of pre-defined steps.

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An Australian Government Initiative
Queensland Government

Background

The novel coronavirus disease, named COVID-19 on 11 February 2020, is caused by SARS-CoV-2 virus. While the number of confirmed cases worldwide and in Australia is reported daily, detailed data on the outcomes of people who test positive for SARS-CoV-2, and predictors of outcomes, are still scarce. Outcomes are likely to vary with context, including according to extensiveness of surveillance and testing, health systems functioning and population characteristics.

Evidence to date has come primarily from overseas countries who were ahead of us in the pandemic, **but not Australia.**

Knowledge gaps in relation to COVID-19

There is limited information to date describing patient characteristics associated with outcomes. We do know there is substantial variation by age, with younger people generally experiencing milder forms of disease, with a greater proportion of those with severe disease or death being older.

Importantly, these data to date have only been based on **hospitalised patients**, and do not include all patients who have been diagnosed with COVID-19 and were managed in the community.

Furthermore, **they do not include Australian data**. Australian-specific and state-specific data are **essential** as outcomes are dependent on a number of region-specific factors including population profile, health system factors and the public health actions taken by individuals and Government.

Study Objectives

The main objectives of the ATHENA COVID-19 STUDY are:

1. To quantify hospital-based outcomes and deaths, including in relation to sociodemographic characteristics and comorbidities as ascertained from hospital AND general practice data.
2. To estimate the strength of association between these outcomes and sociodemographic and health characteristics.

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Queensland Government

Study Sponsor

The Health Innovation, Investment and Research Office (HIIRO) of Queensland Health is responsible for consultation, development and review of State-wide research ethics and research governance policies.

HIIRO provides a central portal of contact for Researchers, HHS Human Research Ethics Committee Chairs and Members, Coordinators, Research Governance Offices/rs and study sponsors seeking advice and direction on ethical and governance issues associated with the conduct of research in Queensland Health.

How can General Practices help with this?

- This is an information pack containing an outline of the study, letters of support from Queensland Health, Primary Health Networks Queensland, and the Royal Australian College of General Practitioners (RACGP).
- Subsequent to this, a project member from our ATHENA COVID-19 Coordination Centre will contact your practice to explain the details of the study and answer any questions you may have.
- We will also let you know if you have a specific patient(s) who have tested positive for COVID-19, and that we will be contacting them to obtain consent for release of their GP data. Only those consented patients' records will be requested.
- If the patient consents, you will be sent a General Practice Data Release request from Queensland Health via a secure method asking to export a once-only copy of the patient health information to Queensland Health in a simple but secure series of pre-defined steps for the ATHENA COVID-19 Study. A simple instructional link will be made available.
- For further information please contact the ATHENA COVID-19 Coordination Centre on: Tel: (07) 4243 4813 or email: ATHENACV19@health.qld.gov.au

Australian National University

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An Australian Government Initiative

Queensland Government

Figure 3A: Letters of support from professional organisations for the ATHENA COVID-19 study

RACGP
Royal Australian College *of* General Practitioners

Healthy Profession.
Healthy Australia.

1 May 2020

Professor Kim Greaves
Sunshine Coast Hospital and Health Services,
Griffith University, and National Centre for Epidemiology and Population Health,
Australian National University
Department: Cardiology

Email: Kim.Greaves@health.qld.gov.au

Dear Prof Greaves,

The Royal Australian College of General Practitioners (RACGP) is writing to express its support for your proposed Descriptive analyses of predictors of outcomes in patients with COVID-19 in Australia project (the COVID-19 Linkage Project).

The RACGP is committed to supporting its members deliver safe and high quality care. We believe the study's aims to describe outcomes in all people diagnosed with COVID-19 in Queensland, over time and in relation to patient characteristics, will be extremely important and valuable for general practice.

The RACGP is Australia's largest professional general practice organisation with over 40,000 members. Our mission is to improve the health and wellbeing of all people in Australia by supporting GPs, general practice registrars and medical students through education, training, developing resources and guidelines, and developing standards that general practices use to ensure high quality healthcare.

Yours sincerely

Roald Versteeg
General Manager
Policy, Practice & Innovation

phn QUEENSLAND

An Australian Government Initiative

22 June 2020

Dear General Practitioner

I write to you on behalf of the seven PHNs across Queensland to express our support for the ATHENA COVID-19 project, a timely new research study examining positive COVID-19 diagnoses. The CEOs endorse this collective letter of support to GPs prepared by Central Queensland, Wide Bay, Sunshine Coast PHN.

The study aims to describe outcomes in all people diagnosed with COVID-19 in Queensland, over time and in relation to patient characteristics, by linking COVID-19 notification, hospital, general practice and death data.

It is essential we collect and analyse Australian- and state-specific data as the epidemic continues, as outcomes are dependent on a number of region-specific factors as well as the public health actions taken by individuals and Government.

The participation of general practice in this study is vital – patient health information collected in the general practice setting contains detailed and up-to-date information on patient characteristics, including health conditions and medications at the time of infection.

ATHENA COVID-19 will be led by Professor Kim Greaves, consultant cardiologist at the Sunshine Coast University Hospital.

In addition to the information provided in this pack, a GP liaison officer from the ATHENA COVID-19 project team will contact individual general practices to further explain the details of the study and inform you if specific patient(s) have tested positive for the virus.

The project team will be contacting patients individually to obtain consent for release of their GP data and GPs will also have the option of contacting patients themselves first to let them know they will be contacted by the project team.

Patient confidentiality is of paramount concern to the PHN, and we are more than satisfied Kim and the project team have ethical methodologies in place and have robust processes to maintain the integrity and safety of any collected data.

This compelling project is moving quickly and aims to approach all patients, analyse all data and have prepared a full report by December 2020.

The main findings of the study will be circulated in RACGP and PHN newsletters, and will no doubt be much anticipated. Your contribution would be highly valued.

I would like to take the opportunity here, again on behalf of PHNs across the state, to thank you for your responsiveness and agility in helping to manage the pandemic so far, and to reaffirm our commitment to supporting general practice wherever we can.

Yours faithfully

Pattie Hudson.

Pattie Hudson
Chief Executive Officer
Central Queensland, Wide Bay, Sunshine Coast PHN
(for and on behalf of PHN Queensland)

Queensland Government

Queensland Health

Enquiries to: Melissa Hagan
Director
QCTCU, HIIRO
Telephone: 0438634329
File Ref: C-ECTF-20/9553

Professor Kim Greaves
Senior Medical Officer, & Director of Cardiac Research
Sunshine Coast University Hospital
Sunshine Coast Hospital and Health Service

Email: Kim.Greaves@health.qld.gov.au

Dear Professor Greaves

I am writing to express my support on behalf of Queensland Health for the **A**ustralians **T**ogether **HE**alth I**N**iti**A**tive (ATHENA) COVID-19 Linkage project, a descriptive analyses of predictors of outcomes in patients with COVID-19 in Australia.

The project aims to describe outcomes in all people diagnosed with COVID-19 in Queensland, over time and in relation to patient characteristics. It is an important study to better understand the implications of COVID-19 and the impact on the Queensland community.

Queensland Health is committed to helping care for Queenslanders and with your collaboration with the Department of Health's Health Innovation and Investment and Research Office (HIIRO), the Australian National University (ANU), the Royal Australian College of General Practitioners (RACGP) and the Department of Health's Primary Health Networks (PHNs), I welcome the findings from this study.

Yours sincerely

Dr Jeannette Young PSM
Queensland Chief Health Officer
and Deputy Director-General
Prevention Division
10 / 07 / 2020

Figure 4A. Letter of support from the National Heart Foundation of Australia acknowledging the impact of the work done as part of this thesis.

Heart Foundation

National Heart Foundation of Australia
ABN 98 008 419 761

For heart health information and support, call our Helpline on **13 11 12** or visit **heartfoundation.org.au**

15 June 2021

To whom it may concern

Professor Kim Greaves has undertaken several research projects related to cardiovascular disease presentation whilst undertaking the degree of Master of Philosophy in Applied Epidemiology at the Australian National University.

His work has resulted in two peer-reviewed publications: *'A Cross-Sectional Survey Describing General Practitioners' Absolute Cardiovascular Disease Risk Assessment Practices and their Relationship to Knowledge, Attitudes and Beliefs about Cardiovascular Disease Risk in Queensland, Australia'*, and *'A Retrospective Cross-Sectional Study Assessing Absolute Cardiovascular Disease Risk Score And Pharmacotherapy At The Time Of Admission In Patients Presenting With Acute Coronary Syndrome Due To Coronary Artery Disease In A Single Australian Tertiary Centre'*.

This work has helped the National Heart Foundation of Australia promote the importance of cardiovascular disease risk assessment and management across Australia to consumers, general practitioners, nurses and other allied health professionals.

Kim's work has been incorporated into general practice education workshops and helped inform the Heart Foundation team on gaps in practice around primary prevention. Kim's work on cardiovascular disease surveillance funded by the Heart Foundation, will also be useful in helping the Foundation understand the importance of cardiovascular disease risk surveillance, and how this may be achieved on a national scale.

I am highly appreciative and supportive of Kim's work, and look forward to future progress in this area.

Yours sincerely

Natalie Raffoul
National Risk Reduction Manager
Heart Foundation

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(02) 6282 5744

Sydney NSW
Level 3,
80 William St
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Darwin NT
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Tiwi NT 0810
(08) 8982 2700

Brisbane QLD
1 Abbotsford Rd
Bowen Hills
QLD 4006
(07) 3872 2500

Adelaide SA
155-159 Hutt St
Adelaide
SA 5000
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Melbourne VIC
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Docklands
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(03) 9329 8511

Perth WA
334 Rokeby Rd
Subiaco
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(08) 9388 3343

Hobart TAS
Level 1,
89 Brisbane St
Hobart
TAS 7000
(03) 6224 2722

MC-CORP-001.2.0120

Figure 5A. Additional related work published during MAE period

Open access Original research

BMJ Open

Absolute cardiovascular disease risk score and pharmacotherapy at the time of admission in patients presenting with acute coronary syndrome due to coronary artery disease in a single Australian tertiary centre: a cross-sectional study

Amy Bailey ,[1] Rosemary Korda,[2] Jason Agostino,[3] Tony Stanton,[1] Gabriela Kelly,[4] Tuppence Richman,[1] K Greaves[1,2]

To cite: Bailey A, Korda R, Agostino J, *et al*. Absolute cardiovascular disease risk score and pharmacotherapy at the time of admission in patients presenting with acute coronary syndrome due to coronary artery disease in a single Australian tertiary centre: a cross-sectional study. *BMJ Open* 2021;**11**:e038868. doi:10.1136/bmjopen-2020-038868

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-038868).

Received 27 March 2020
Revised 21 August 2020
Accepted 09 October 2020

For numbered affiliations see end of article.

Correspondence to
Professor K Greaves;
kim.greaves@health.qld.gov.au

ABSTRACT

Objectives To describe (1) absolute cardiovascular disease risk (ACVDR) scores in patients presenting to hospital with acute coronary syndrome (ACS) and (2) proportions of these patients on guideline-recommended pharmacotherapy according to their ACVDR score.

Design Cross-sectional study.

Setting Single-site tertiary centre hospital, Queensland, Australia over a 12-month period.

Participants Patients >18 years of age presenting to hospital with ACS due to coronary artery disease (CAD) confirmed by angiography.

Primary and secondary outcome measures Proportion of patients without prior history of CVD with a high ACVDR score, and of patients with a prior history of CVD, who are on guideline-recommended pharmacotherapy.

Results 527 ACS patients were included of whom the mean age was 63 years and 75% were male. Overall, 66% (350) had no prior CVD and 34% (177) patients had prior CVD.

In patients with no prior CVD, the proportions of patients with low, intermediate and high CVD risk scores were 41%, 24% and 36%. In the no prior CVD, high-risk patient group, 48% were on no preventative pharmacotherapy, 32% on single pharmacotherapy and 20% patients on complete guideline-recommended pharmacotherapy. In the prior CVD group, 7% patients were on no pharmacotherapy, 40% on incomplete pharmacotherapy and 53% were on complete guideline-recommended pharmacotherapy.

Conclusion This study adds to the evidence on implementation gaps in guideline-recommended management of ACVDR, showing that a large proportion of patients presenting with ACS due to CAD were at high risk of developing CVD prior to the event and most were not on guideline-recommended treatment. A significant proportion of these events are likely to have been preventable, and therefore, increased assessment and appropriate treatment of ACVDR in primary care is needed to reduce the incidence of CVD events in the population.

Strengths and limitations of this study

- ► First survey to report the absolute cardiovascular disease risk (ACVDR) scores in patients presenting with acute coronary syndromes to hospital and the proportions of these patients on guideline-recommended pharmacotherapy in relation to their ACVDR score.
- ► Adds to evidence that many Australians at high CVD risk are not receiving recommended combination therapy.
- ► Limited to single centre in Queensland, Australia.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Australia, and its prevention is a National Health Priority.[1 2] In Australia, CVD accounted for 27% of all deaths in 2017 and was the main cause of hospital admissions.[2 3] A large proportion of CVD is preventable by appropriate population-level interventions and individual management of risk.[3] The National Vascular Disease Prevention Alliance of Australia recommends calculating risk using the absolute cardiovascular disease risk (ACVDR) Score.[4–6] A 5-year risk for the development of CVD is calculated and categorised according whether a patient is low (<10%), moderate (10%–15%) or high risk (>15%). Preventative medication is recommended if the ACVDR is higher than 15%, or 10%–15% with other risk factors. Recommended primary preventative pharmacotherapy consists of prescription of both a cholesterol-lowering and an

antihypertensive agent.[4] For patients with prior CVD, the recommended secondary prevention consists of three agents: an antiplatelet agent such as aspirin (or anticoagulant if indicated), a statin and an antihypertensive triple therapy.[5]

Despite clear guidelines, most Australians at high CVD risk are not receiving recommended combination therapy. This treatment gap is likely multifactorial, including underutilisation of CVD risk calculators.[7–10] The undertreatment of patients at high CVD risk results in a significant missed opportunity in the prevention of cardiovascular events. To date, there are limited Australian data demonstrating gaps in implementation of guidelines and hence missed opportunities for prevention. In particular, there are no studies that have quantified CVD risk scores and appropriateness of pharmacological treatment at the time of patient presentation to hospital with acute coronary syndrome (ACS).

This study aimed to report: (1) the ACVD risk scores in patients presenting to hospital with ACS due to coronary artery disease (CAD) and (2) the proportions of these patients according to their risk, on guideline-recommended pharmacotherapy.

METHODS

Study design and population

This study was a cross-sectional study of patients presenting with ACS to a single tertiary hospital in Australia over a 12-month period from 1 November 2016 to 31 October 2017. All patients over 18 years of age presenting with ST-elevation myocardial infarction (STEMI) or non-ST elevation MI (NSTEMI) with type 1 MI (defined by the Fourth Universal definition of MI), and who underwent coronary angiography demonstrating significant CAD (defined as at least one lesion of ≥50% stenosis) were included.[11] Patients with unstable angina were also included and defined as ischaemic sounding chest pain with significant coronary disease. Patients were excluded if they presented with ACS but did not undergo coronary angiography or where the discharge diagnosis was not thought due to atherosclerotic coronary artery disease such as a type 2 MI (spontaneous coronary artery dissection, Takotsubo cardiomyopathy, MI with non-obstructive coronary artery disease on angiography or myocarditis).

Data collection and variables

Demographic and health data were collected from patient's non-anonymised medical records and included information on past medical history of ischaemic heart disease, peripheral vascular disease, cerebrovascular events, diabetes mellitus, hypercholesterolaemia and hypertension, as well as smoking status.

Blood collected during the first 24 hours of admission was used to identify renal function and document HbA1c and lipid profile for risk factor calculation. Patients without a noted history of diabetes mellitus but with an HbA1c>6.5% on admission were considered to have diabetes mellitus for risk calculation.[6] As per guidelines, patients were considered to be at automatic high risk if the total cholesterol ≥7.5 mmol/L, systolic blood pressure (BP) ≥180 mm Hg or diastolic BP ≥110 mm Hg, glomerular filtration rate was <45 mL/min/1.73 m^2 or a previous diagnosis of familial hypercholesterolemia was documented.[6] Data regarding diabetes with microalbuminuria were not available. Patients were recorded as having a family history of CVD if documented in the notes by the treating physician.

Medication use at admission was collected from the patient medical record, which includes self-reported medication use as well as, where available, pharmacist admission history which cross references self-reported medication use with general practitioner prescriptions and pharmacy dispensing history for increased accuracy.

Calculation of absolute cardiovascular disease risk scores

Patient were classified into two groups based on their history of cardiovascular disease. Prior CVD was based on a history of CVD defined as a reported history of ischaemic heart disease, ischaemic cerebrovascular disease or peripheral vascular disease. In patients with no prior CVD, the online Australian ACVDR calculator was used to determine the patient's risk of a CVD event in the next 5 years: low (<10%), intermediate (10%–15%) or high (>15%).[6] This calculator requires identifying clinically determined high CVD risk based on sex, age, systolic BP, smoking status, total cholesterol, high-density lipoprotein cholesterol, diagnosis of diabetes and evidence of left ventricular hypertrophy on ECG (online supplemental figure 1).[7] The systolic BP used for this calculation was a mean of two recordings taken as the first recordings in a ward setting when the patient was pain free and before to the initiation of new medical therapies (wherever possible). An ECG diagnosis of left ventricular hypertrophy was based on Sokolow-Lyon criteria.[12] The ACVD risk calculator was developed for patients not on preventative medical therapy and scores have not been validated in those on treatment. For the purposes of our study, it is valid to assume that those found to be at high risk despite being on preventative therapy, are still high risk. This approach has been used in previous studies.[13] 'Low' and 'moderate' risk scores were also calculated despite a proportion of these patients (see results) taking cholesterol-lowering and/or antihypertensive medication (see the Discussion, Limitations section).

Analysis

Data were described separately according to prior CVD (with/without), with continuous variables reported as means and SD and categorical variables as counts and proportions. Although non-anonymised data were used to collect patient information and variables, this was then deidentified for analysis and storage.

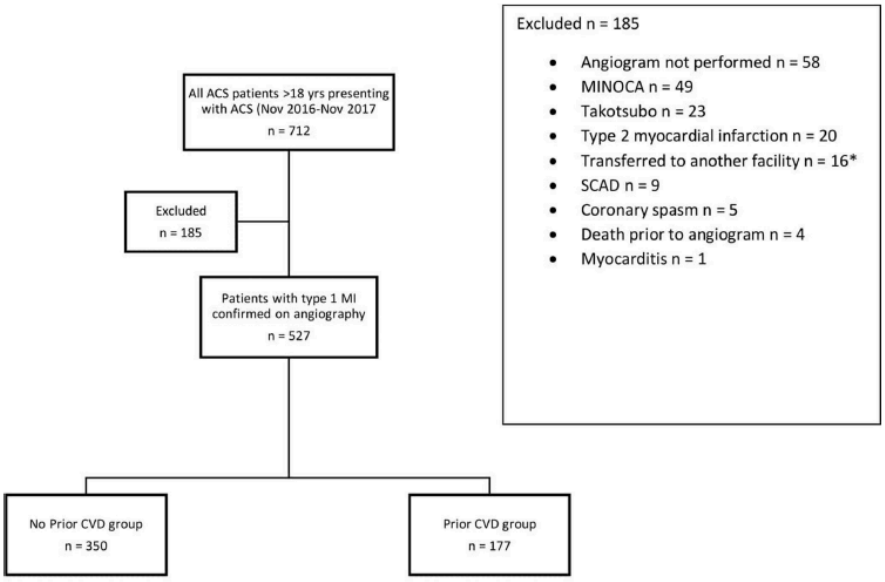

Figure 1 Study population. A history of cardivascular disease (CVD) defined as reported history of ischaemic heart disease, ischaemic cerebrovascular disease or peripheral vascular disease. *These patients had a private healthcare cover and chose to be transferred to private hospitals for their ongoing investigation and management. ACS, acute coronary syndrome; MI, myocardial infarction; MINOCA: myocardial infarction with nonobstructive coronary arteries; SCAD: spontaneous coronary artery dissection.

RESULTS

Patient characteristics

From November 2016 to October 2017, 712 patients presented with an ACS. Of these 185 (26%) were excluded from analysis, the key reasons being that the patient did not undergo angiography (n=58), no significant coronary artery disease was found on angiography (n=49) or the diagnosis was considered takotsubo cardiomyopathy (n=23) (figure 1). The remaining 527 patients included in the study were composed of 350 (66%) patients with no prior CVD, and 177 (34%) patients with prior CVD.

In the no prior CVD group, the mean age was 63 years, 75% were male, 54% presented with an STEMI, 39% with NSTEMI, and 7% with unstable angina (table 1). In regard to risk factors, 29% were current smokers, 39% had a family history of premature cardiovascular disease, 21% had diabetes, 34% hypercholesterolaemia and 50% a history of hypertension.

The prior CVD group most commonly had a history of ischaemic heart disease (82%) rather than peripheral vascular disease (11%) or cerebrovascular disease (18%). In regard to risk factors, there were lower rates of current smokers (18%), however, there were high rates of other comorbidities including hypertension (78%), chronic kidney disease (11%), diabetes (24%) and hypercholesterolaemia (70%).

Patients with no prior CVD (primary prevention)

Figure 2 shows the proportions of patients in the different ACVD risk score categories including those with and without prior CVD. Out of 350 patients with no prior CVD, 26 (7%) patients had missing data and CVD risk could not be calculated. Of the remaining 324 (93%), 41% were low risk, 24% intermediate risk and 35% at high risk of a CVD event.

In those at high risk, 48% were not on any preventative therapy, 32% were on single preventative therapy and 20% were on both lipid-lowering and antihypertensive therapy. Of the latter group, four patients not previously known to be diabetic were found to have diabetes based on elevated admission HbA1c values and were not on antiglycaemic therapy. Therefore overall, one in five patients at high primary CVD risk (20%) were on complete guideline-recommended primary preventative therapy (figure 3).

In both the low and moderate risk groups, 57% were not on any preventative therapy, 29% and 32% were on single preventative therapy, and 14% and 11% were on both lipid-lowering and anti-hypertensive therapy, respectively (online supplemental figure 2).

Patients with prior CVD (secondary prevention)

Among the 177 patients with prior CVD (figure 2), 7% were not on any treatment at the time of admission, 8%

Table 1 Sample characteristics: acute coronary syndrome patients with and without prior CVD

	No prior CVD group n=350	Prior CVD group n=177
Age—years	63.1±12.0	70.5±10.1
Male sex—no (%)	263 (75.1)	135 (76.3)
BMI	28.4±5.1	28.4±5.1
Total cholesterol—mmol/L	5.3±1.4	4.3±1.4
HDL—mmol/L	1.1±0.3	1.1±0.3
LDL—mmol/L	3.3±1.2	2.5±1.2
Systolic BP—mm Hg	129.8±18.4	132.3±18.0
Diastolic BP—mm Hg	76.8±11.1	73.6±9.7
Left ventricular hypertrophy on ECG	24 (6.6%)	–
Smoking status		
Never smoker	121 (34.6%)	66 (37.3%)
Ex-smoker	123 (35.1%)	76 (42.9%)
Current smoker	103 (29.4%)	31 (17.5%)
History of		
Family history of CVD	136 (38.9%)	57 (32.3%)
Rheumatoid arthritis	3 (0.9%)	0
Chronic kidney disease	11 (3.1%)	20 (11.3%)
Diabetes	72 (20.6%)	43 (24.3%)
Hypercholesterolaemia	120 (34.3%)	124 (70.1%)
Hypertension	174 (49.7%)	138 (78.0%)
Prior CVD		
IHD		145 (81.9%)
PVD		20 (11.3%)
CVA		32 (18.1%)
Type of acute coronary syndrome		
STEMI	188 (53.7%)	48 (27.1%)
NSTEMI	138 (39.4%)	94 (53.1%)
UA	24 (6.9%)	35 (19.8%)
Management after angiography		
Medical treatment	21 (6.0%)	44 (24.9%)
PCI	286 (81.7%)	109 (61.6%)
CABG	43 (12.3%)	23 (13.0%)

SD given. STEMI.
BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CVA, cardiovascular accident; CVD, cardiovascular disease; IHD, ischemic heart disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

were on a single agent (statin, antihypertensive or antiplatelet/anticoagulant), 32% on dual therapy and 53% on guideline-recommended triple therapy. Of these, six were diabetic and not on antiglycaemic medication. Therefore, among patients with prior CVD, approximately half were on optimal guideline-recommended pharmacotherapy (figure 3).

DISCUSSION

In this study, one-third of the patients with no prior CVD presenting with ACS were found to have a high ACVD risk score, and of these, only one in five were on appropriate guideline-recommended pharmacotherapy. Among those patients with prior CVD and ACS, only half were receiving guideline recommended pharmacotherapy. Importantly, the majority of patients (two-thirds) presenting with ACS due to CAD, had no prior history of CVD.

All major CVD prevention guidelines use some method of risk factor assessment to calculate estimated risk for developing cardiovascular events with subsequent prescription of lifestyle and medication to reduce this risk.[14–16] Previous studies have shown both the under-recognition of these patients and the undertreatment, with the majority of research in this areas focused on the primary care setting.[10 13 17] In contrast, this study describes the risk profiles and associated preventative therapies among patients presenting with ACS, which has not previously been reported on in an Australian population.

An estimated 80% of CVD events are preventable by intervening to reduce risk.[18 19] Absolute CVD risk assessment and management is current best practice and recommended for ages 45–74 years in Australia.[4] Reductions in BP and lipids using standard treatments are able to halve risk but previous research suggests that 76% of Australians at high primary CVD risk are not receiving these basic best practice preventive therapies.[13 20] This evidence is supported by our study which showed that one-third of patients presenting with ACS and no prior history of CVD, were at previously at high risk of developing CVD, and of these 80% were not on correct preventative pharmacotherapy. In those patients with prior CVD presenting with ACS, approximately half are not on correct pharmacotherapy.

There are likely multiple reasons for the underutilisation of preventative medication recommended by evidence-based guidelines on primary and secondary prevention.[9 21] These include the underutilisation of risk calculators, reluctance to prescribe medication and reliance on lifestyle measures and poor medication compliance.[10 17 22] Heeley showed that only 60% of general practitioners reported utilising cardiovascular risk calculators.[10] Additionally, when general practitioners (GPs) were asked to estimate patients' risk of CVD events, the perceived risk was often underestimated—even patients with established CVD, 60% were thought to be low or intermediate risk.[10] A further difficulty is that for those patients who are appropriately assessed and prescribed CVD preventative medications, the adherence to medications is poor at 50% compliance for patients where the

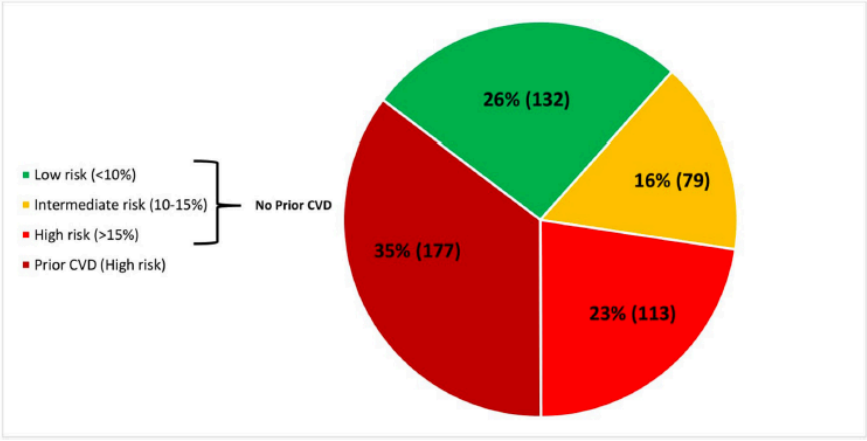

Figure 2 Australian cardiovascular disease risk (ACVDR) scores categories in patients presenting to hospital with acute coronary syndrome due to coronary artery disease. ACVDR Score: a 5-year risk for the development of CVD which is categorised according whether a patient is low (<10%), moderate (10%–15%) or high risk as shown by pattern red. Prior CVD: a history of CVD or peripheral vascular disease. Note that in 26 patients ACVDR score could not be calculated and these have been excluded from analysis. CVD, cardivascular disease.

indication is primary prevention and 66% for those with a history of cardiovascular disease.[23]

This study is important because it shows that the majority of high CVD risk patients who suffered an ACS due to coronary artery disease were not on the preventative therapy. According to guidelines, appropriate treatment of patients with high CVD risk will reduce future adverse cardiovascular events.[14 15] This suggests that in our study, for those patients who were found at presentation to be at high CVD risk and not on appropriate pharmacotherapy, a significant proportion of these adverse events could potentially have been avoided if preventative therapy had been previously instigated. This data from this study presents a highly persuasive argument to

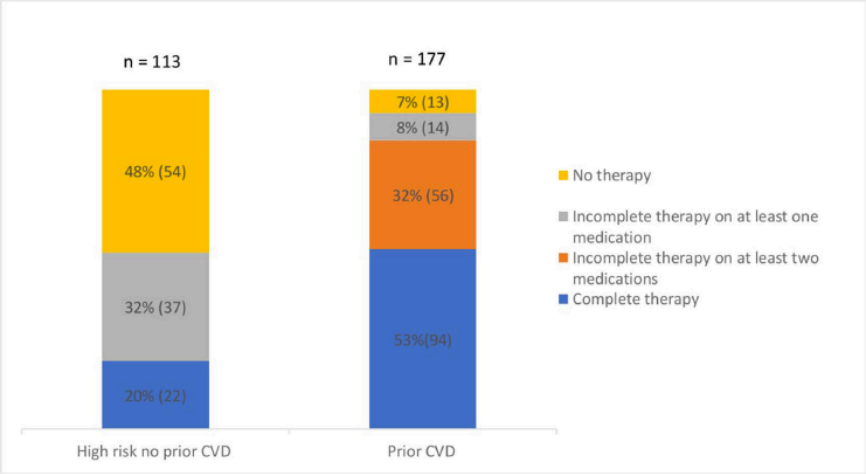

Figure 3 Proportions (%) and numbers of patients presenting with acute coronary syndrome due to coronary artery disease in the high risk no prior cardiovascular disease and prior cardiovascular disease groups or guideline-recommended pharmacotherapy. ACVDR Score: a 5-year risk for the development of CVD which is categorised according whether a patient is low (<10%) or high risk (>15%). Prior CVD: a history of CVD defined as reported history of ischaemic heart disease, ischaemic cerebrovascular disease or peripheral vascular disease. Note that in 26 patients AVCDR score could not be calculated and these have been excluded from analysis. ACVDR, absolute cardiovascular disease risk; CVD, cardiovascular disease.

both patients and GPs alike that ACVD risk assessment and appropriate early treatment is essential if the development of CVD is to be prevented.

Strengths and limitations of this study

The strength of this study is that it only included consecutive patients who had ACS due to coronary artery disease. Participants (STEMI and NSTEMI) had to have a type 1 MI defined by acute myocardial injury and significant CAD on coronary angiography. Those patients who had unstable angina had to have ischaemic chest pain and evidence of significant CAD on coronary angiography.

There are several limitations in this study that should be considered. First, this was a small volume single centre study which may reflect a unique demographic or prescribing practice. In terms of representativeness, however, the Sunshine Coast appears to be ranked roughly mid-way in terms of heart-related hospital admissions and coronary heart disease mortality rates compared with the rest of the country.[24] Second, data were derived from written medical records, self-reported medical history and discharge summaries which may not always reflect accurately what happened during the admission. Third, calculation of CVD risk using the ACVDR score requires systolic BP for calculation. Ideally BP should be recorded as a mean of two readings taken after sitting for 5 min in a quiet room before antihypertensive medication is given and avoids the problem of recording overly high BP readings.[4] This is not always possible in an acute hospital environment, and the compromise in this study was to take the mean of two BP recordings in a ward setting. To our advantage all patients admitted to our hospital are given their own single room meaning their environment is quiet. The BP was also recorded where possible before the initiation of antihypertensive medication. For those patients where an antihypertensive medications had been given which was rare, the systolic BP may have been lower and CVD risk underestimated.

In addition, a proportion of patients in the low and moderate risk groups were receiving primary preventative therapies which may have reduced risk as calculated by the ACVDR calculator which is intended to be used in treatment naïve patients.[4 6] Therefore, interpretation of these results should be undertaken with caution.

However, the focus of this study was on those known to be at high risk. Those patients who experienced out-of-hospital cardiac arrest due to CAD and did not survive to hospital—this group along with their risk scores, are not represented in this study. This study did not ascertain why patients were not on the correct medications. It would be useful to know the reasons why and what proportions of patients were unbale to (eg, unable to tolerate) or actively decided not to take their prescribed medications. This information would be helpful for benchmarking targets in the surveillance of ACVDR score and appropriateness of treatment across populations. The proportions of patients presenting with ACS within the low and intermediate risk groups may appear at first glance, disproportionately high with respect to their overall risk. However, this assumption is incorrect. In order to estimate the true proportions of patients presenting with ACS from the low and moderate risk groups one would need to know the denominator for each risk category that is, the number of patients in each at-risk population from which the ACS patients presented and is not available. Furthermore, a proportion of the patients in these low and moderate risk groups were on anti-hypertensive and cholesterol-lowering medication. Therefore, in these patients the calculated risk scores are likely to be lower than their true risk. For these reasons, this study has predominantly focused on the high risk group only.

Conclusion

A large proportion of patients presenting with ACS were previously at high risk of developing CVD and the vast majority were not on guideline-recommended treatment. A significant proportion of these adverse events could have been potentially avoided if preventative therapy had been previously instigated. Increased assessment and appropriate treatment of ACVDR by GPs needs to increase if CVD events are to be reduced.

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intellectual content and gave final approval of the version to be published; JA agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KG: made substantial contributions to the conception or design of the work; the acquisition, analysis and interpretation of data for the work; he revised it critically for important intellectual content and gave final approval of the version to be published; KG agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethics approval for this study was granted by The Prince Charles Hospital Human Research Ethics Committee (HREC/18/QPCH/43).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Release of data was not covered by ethics approval and therefore is not able to be provided.

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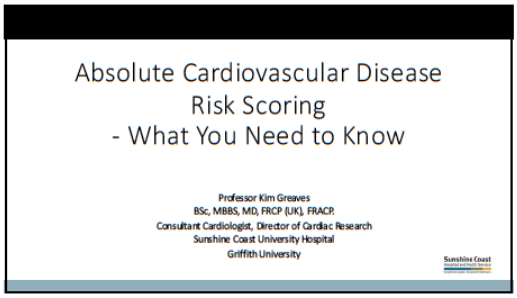
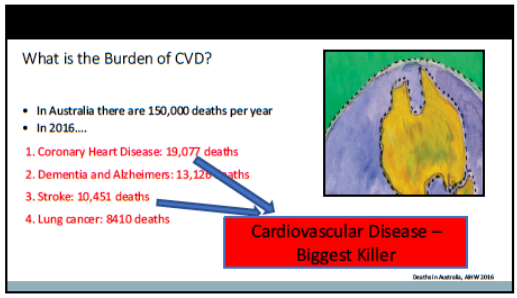
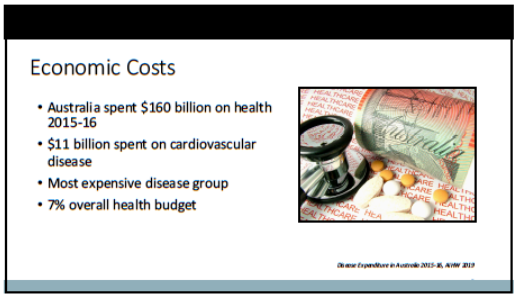
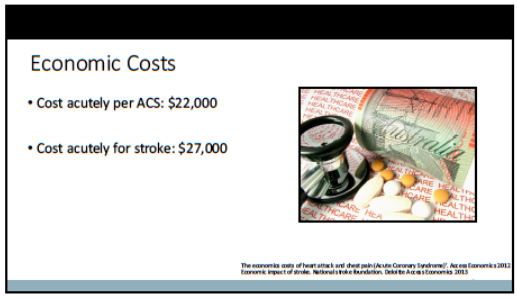
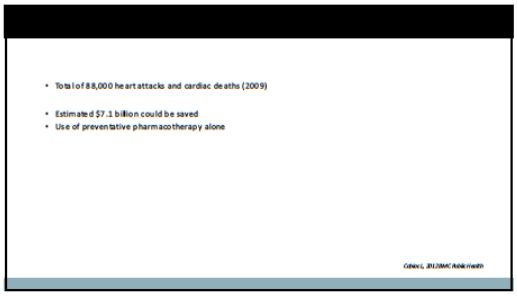
Figure 6A. Slide presentation at a national conference: National Primary Health Network conference, Sydney 2019.

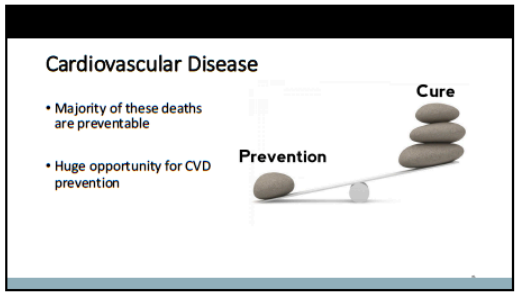












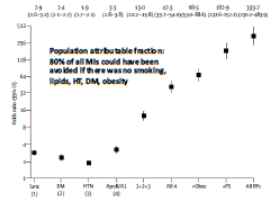
Evidence that Cardiovascular Disease is Preventable

Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study

Yusuf Lancet 2004

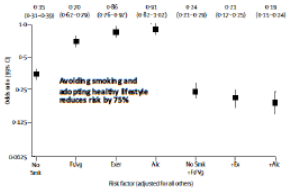
- 52 countries
- 15,152 MIs and 14,882 controls
- Relationship between risk factors and MI
- Population attributable fraction

Risk of acute myocardial infarction associated with exposure to *multiple* risk factors

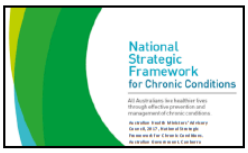


Interheart Study, Yusuf et al Lancet 2004

Risk of acute myocardial infarction associated with potentially protective risk factors



Interheart Study, Yusuf et al Lancet 2004

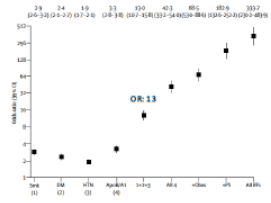


Prevention of CVD is a National Health Priority

Combined Risk

- Rather than treating individual risk factors
- Overall effect of multiple individual risk factors
- Combined together
- Create a more accurate picture or *score*
- Individuals overall future risk of having a heart attack or stroke

Risk of acute myocardial infarction associated with exposure to multiple risk factors



Interheart Study, Yusuf et al Lancet 2004

Absolute Cardiovascular Disease Risk Score Assessments

- National Vascular Disease Prevention Alliance
  - 45 years or over
  - 35 years or over & Aboriginal or Torres Strait Islander
  - Without history of cardiovascular disease
- ➜ Absolute Cardiovascular Disease Risk checked
- Calculate likelihood of heart attack, stroke, vascular disease in next 5 years

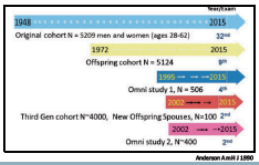
Cardiovascular disease risk profiles

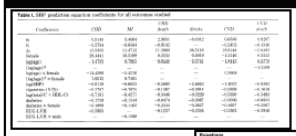
Kooren M. Anderson, PhD, Patricia M. Odell, PhD, Peter W. F. Wilson, MD, and William B. Kannel, MD, MPH *Framingham and Boston, Mass.*

This article presents prediction equations for several cardiovascular disease endpoints, which are based on measurements of several known risk factors. Subjects (n = 5573) were original and offspring subjects in the Framingham Heart Study, aged 30 to 74 years, and initially free of cardiovascular disease. Equations to predict risk for the following were developed: myocardial infarction, coronary heart disease (CHD), death from CHD, stroke, cardiovascular disease, and death from cardiovascular disease. The equations demonstrated the potential importance of controlling multiple risk factors (blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, glucose intolerance, and left ventricular hypertrophy) as opposed to focusing on one single risk factor. The parametric model used was seen to have several advantages over existing standard regression models. Unlike logistic regression, it can provide predictions for different lengths of time, and probabilities can be expressed in a more straightforward way than the Cox proportional hazards model. (Am Heart J 1990;121:293-8.)

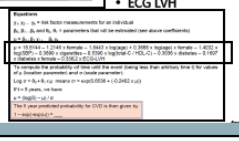
Framingham Risk Equation

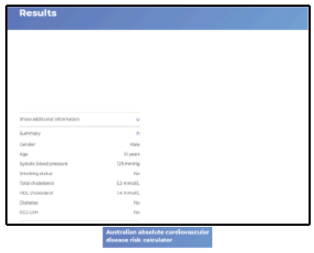
- N=5573 free of CVD
- 30-74 years
- Follow up 4-12 years

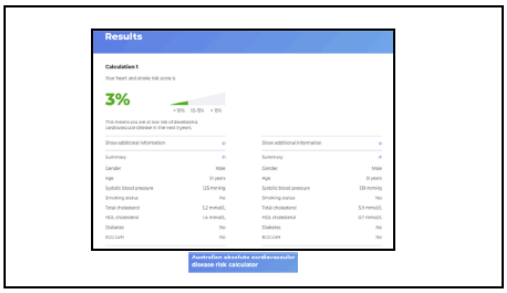




- Age
- Gender
- Systolic BP
- Smoking
- Total chol/HDL ratio
- Diabetes
- ECG LVH





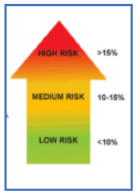


FRE: Advantages and Disadvantages

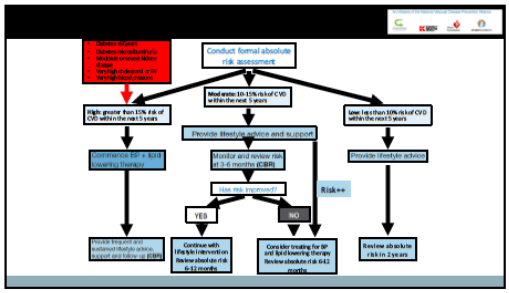
- Most thoroughly tested
- Tested against Australian study performed well
- FRE equivalent or better predictive abilities than other risk scores

- Last century
- Another country
- No FH, obesity, SE status
- No AF
- <74 yrs
- Indigenous
- Patients on meds
- Overestimate risk

Absolute Cardiovascular Disease Risk



- High risk
  - Over 15% (1:7) chance of getting heart attack, stroke, vascular disease in next 5 years
- Moderate risk
  - 10-15% (1:10) chance in next 5 years
- Low risk
  - Less than 10% in next 5 years

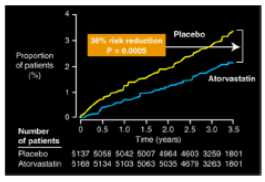


What is the Evidence Interventions Work?

Dual therapy: anti-hypertensive and statin therapy

ASCOT-LAA STUDY

- 19,342 hypertensive patients
- 40-79 yrs & ≥3 other CVD risk factors
- 10,305 into statin study
- 10mg atorvastatin or placebo
- Follow up 5 years for non-fatal MI and fatal CHD
- Stopped trial after 3 years
  - 100 events in atorvastatin group
  - 154 events placebo



Absolute Cardiovascular Disease Risk

What is the uptake of absolute cardiovascular disease risk assessment?

Research

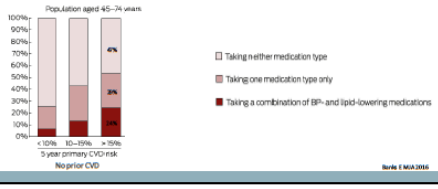
Absolute risk of cardiovascular disease events, and blood pressure- and lipid-lowering therapy in Australia

- N=9564 from 2011-2012 Australian Health Measures Survey
- Calculated ACVDR scores
- Information on medications taken
- Proportions on guideline-recommended therapy
- Estimates for the Australian population

Banks MJA 2016

- There are 7.3M Australians between 45-74 years
- 1.45M of these are at **high** CVD risk (20%)
  - 811,000 people no prior CVD
  - 634,000 people prior CVD

Pharmacological treatment of ACVD risk in Australia



Banks E MJA 2016

- **970,000 at high ACVD risk** (13% of population aged 45-74 yrs)
- **Not receiving guideline-recommended therapies**

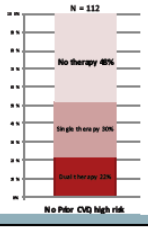
Banks E MJA 2016

ACVD Risk Of Patients Presenting With ACS and their Pharmacological Treatment

- Assessed the ACVD risk score
- Patients presenting with ACS
- 12 months
- 520 patients

Sunshine Coast

ACVD Risk Of Patients Presenting With ACS on Pharmacological Therapy



Why is there such Poor ACVD risk assessment uptake?

Barriers	Enablers
No incentives	Financial opportunities
Time constraints	Clear guidelines
Not useful/no value	
Too many guidelines	
Don't know how to use	
Don't know how to proceed after risk assessment	
Don't think about it	
Low patient compliance	

EURIKA study Eur J Prev Cardiol 2011
Graham et al ESC 2008
Spositio Curr Med Res Opinion 2009

Absolute Cardiovascular Risk Assessment In General Practice: A General Practitioner survey of assessment practices, knowledge attitude and beliefs, and barriers and enablers to assessment

Greaves K 2019

- 111 GPs
- ACVD risk assessment *rates*
  - Categorized:
    - *high assessors (≥ 80%),*
    - *moderate assessors (60-79%)*
    - *low assessors(≤59%)*
- Association between assessment rates and factors related to
  - Practitioner demographics/characteristics
  - GP knowledge/beliefs, patients, organization and structure

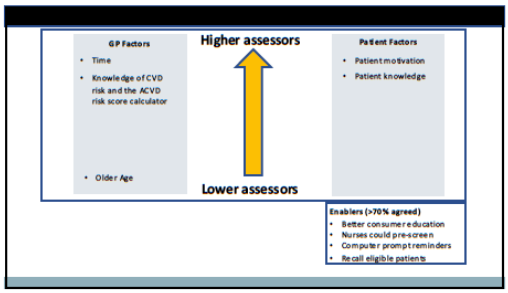
Results

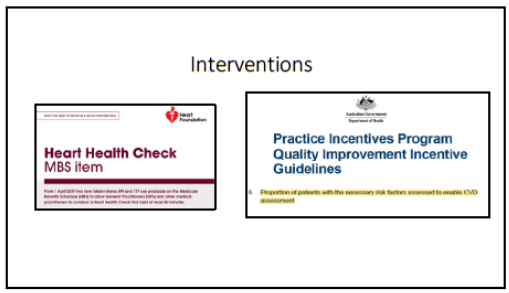
Male		53%
Age >45yrs		43%
Aware of concept of CVD risk		96%
Unaware that CVD risk should be assessed in all eligible patients		11%
Used Australian CVD risk calculator		71%
Used own clinical judgement, didn't use any score, or didn't know		9%
Time spent explaining what score means	0-4 mins	28%
	5-9 mins	48%
	10-15 mins	15%

Results

Group	Assessment rates
High assessors (≥ 80%)	45%
Moderate assessors (60-79%)	25%
Low assessors (≤59%)	23%
Very low (<19%)*	10%
Very high (100%)	17%

* did not assess risk, treated risk factors individually or were unsure who an eligible patient was.





Importance of Surveillance

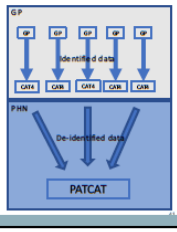
- Surveillance system is essential to:
  - To quantify the magnitude and distribution of a disease
  - To monitor effectiveness of prevention strategies
  - To inform public health policy and planning

PenCS

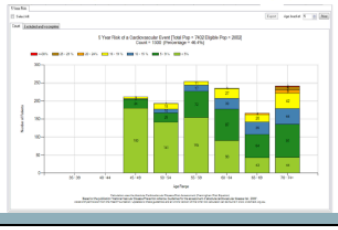
- Australia's majority provider of health analytics software
- 28/31 PHNs
- Monthly reporting on
  - 15 million patients

PATCAT (Practice Aggregation Tool)

- Product of PenCS
- Extracts de-identified data
- Aggregates data
- Reporting tool for population health analysis
- Possible surveillance tool for ACVD risk over a population



PAT CAT: proportions of ACVDR in a GP population



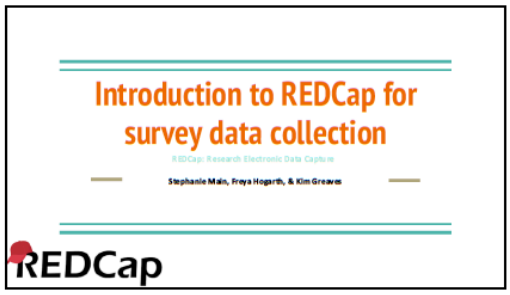
Study Objectives

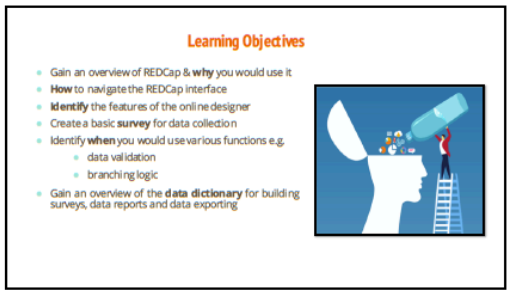
- To evaluate PAT CAT as a *surveillance system* for monitoring
- Levels of absolute CVD risk and treatment within population

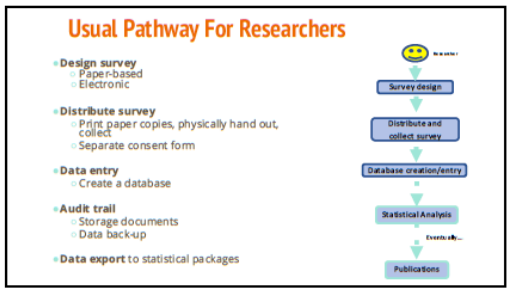
Conclusions

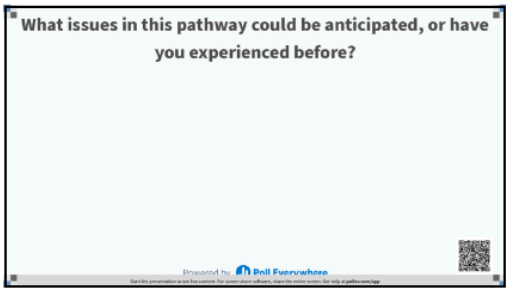
1. CVD is a serious health problem
2. CVD largely preventable
3. Absolute CVD risk assessment indicates an individual's *overall* CVD risk
4. Patients should be offered lifestyle modification and pharmacological treatment according to their ACVD risk
5. Current ACVD assessment rates are low
6. A large proportion of people are at high or moderate CVD risk and remain untreated
7. Many of these will go on to have adverse cardiovascular events within 5 years

Figure 7A. Slides used from teaching to MAE students on REDCap









What is REDCap?

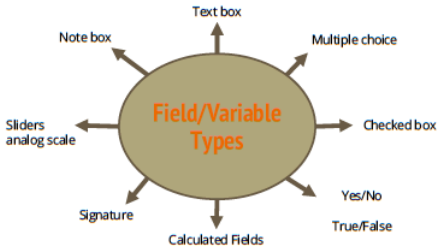
- Research Electronic Data CAPture
- Secure, web-based data collection system
- Built by Vanderbilt University in USA
- Widely used by academic community
- Collaborative international network of thousands of intuitions

Why use REDCap?

- Web-based and mobile app
- Data security
  - compliant with Australian legislation
  - better than MS excel and Survey Monkey
- View in real-time data entry
- Intuitive & easy-to-use interface
- Many features e.g. longitudinal data collection and multi-site access with user access rights

Types of REDCap projects

1. **Data entry forms**
   Data collection is performed only by study team
1. **Surveys**
   Data collection is performed by the study participants
1. **Mix of both**



Example of REDCap project

REDCap Survey Development Exercise

- Break out rooms - 2 groups, 20 minutes
- As a group create 5 questions collecting data on a participants:
  - First Name
  - Last Name
  - Gender
  - DOB
  - Email address
- In the exercise we will cover how to:
  - Log in
  - Create a new project
  - Navigate to Project landing page
  - Create your survey in online designer

Discussion

Data Dictionaries

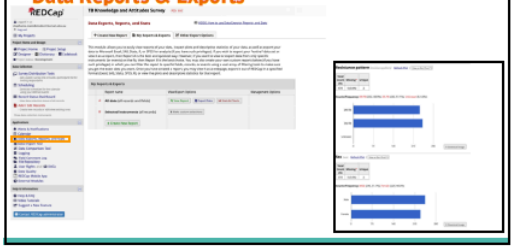
- CSV (Excel) file that holds the architecture of a project.
- Projects can be built or edited in a Data Dictionary, then uploaded into REDCap.
- **Benefits:** more efficient to build and make changes to surveys, and easier to share and collaborate with colleagues

Data Dictionary Example

Resources: The Data Dictionary (10 min)

https://healthinstitute.illinois.edu/sites/default/files/How_to_Use_a_Data_Dictionary.pdf

Data Reports & Exports



Data Reports & Exports

Extra Resources

- https://rsph-redcap.anu.edu.au/
- https://redcap.vanderbilt.edu/plugins/redcap_consortium/training_materials.php


Any Questions? Is there anything else you want to know or learn?
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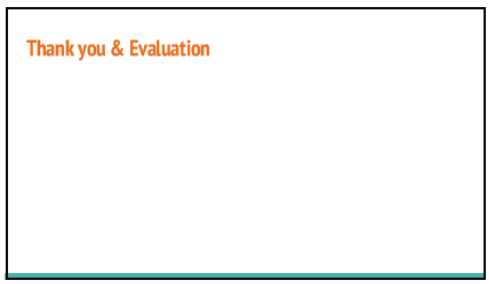

Thank you & Evaluation

Figure 8A. Feedback evaluation from teaching MAE students on REDCap

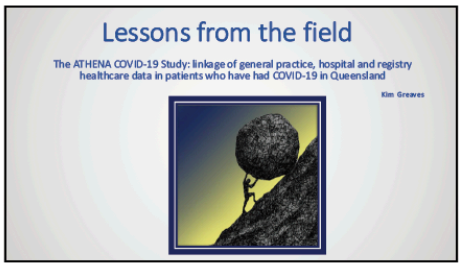
Table 1. Summary of evaluation of individual sessions showing responses of strongly agree and agree*
(Response options were: strongly agree, agree, neither agree or disagree, disagree, strongly disagree)

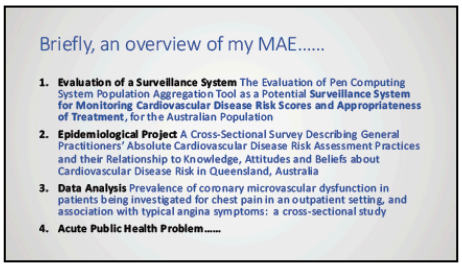
	Lesson 1 – AMR and HAI N=20		Lesson 2 – COVID-19 vaccines N=18		Lesson 3 – REDCap N=13		Lesson 4 – First Nations and CALD N=13	
	Strongly agree (%)	Agree (%)	Strongly agree (%)	Agree (%)	Strongly agree (%)	Agree (%)	Strongly agree (%)	Agree (%)
The facilitators were prepared and organised	30	60	40	56	92	8	83	17
The learning objectives were outlined at the beginning of the session	65	30	44	50	77	23	75	25
The content presented was relevant to my knowledge and understanding of epidemiology and public health	45	45	56	39	92	8	67	33
I feel motivated to learn more about this subject area after the session	40	40	56	39	77	23	42	58
The facilitator's teaching methods and aids were appropriate and effective to my learning	50	40	33	50	85	15	75	25
The facilitators provided opportunities to ask questions and participate in further discussion	50	45	44	50	77	23	42	58
At the end of the session, the learning objectives were met	35	55	50	44	77	23	75	25
Overall, I am very satisfied with the session	40	50	61	33	85	15	75	25
The facilitators listened to me and respected my previous experiences in this area#							42	17

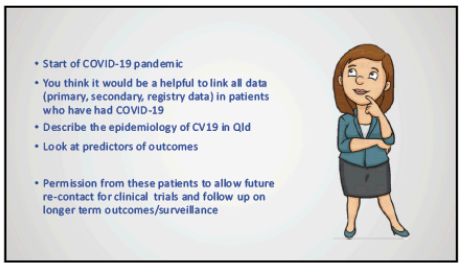
* Some totals are more than 100% as numbers were rounded up

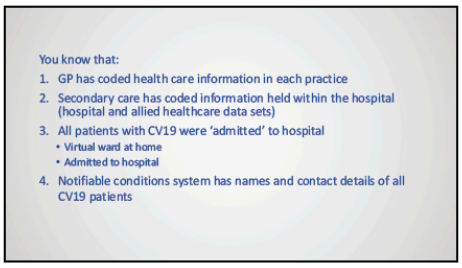
This statement was only included into the evaluation for lesson 4

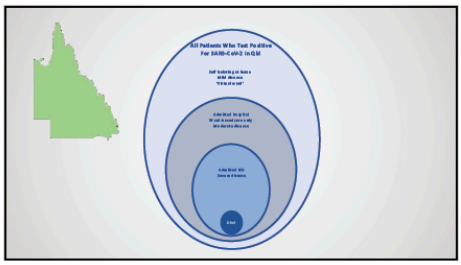
Figure 9A. Slides used from 'Lessons from the field'

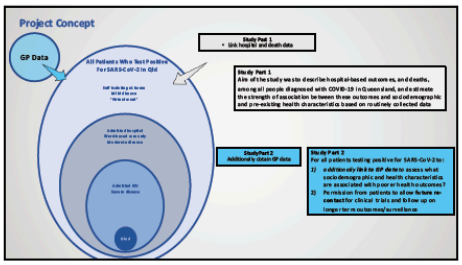










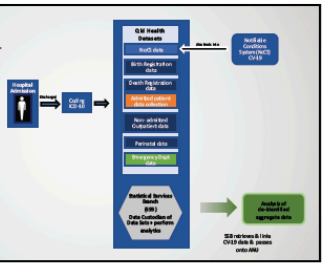


- Divide the project into **two parts:**
  - **Study Part 1** links Queensland COVID-19 notification, hospital and death registry data
  - **Study Part 2** links Queensland COVID-19 notification, hospital and death registry data, as well as patient's healthcare information held within general practice.

Study Part 1

- How would you go about this?

Study Part 1

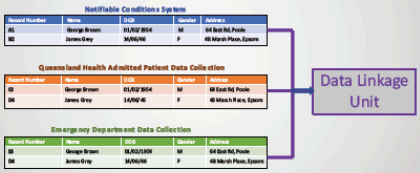


Steps

1. Ethics approval
2. Request Director-General Queensland Health under the Public Health Act
3. Give permission to allow access to CV19 patient data in Queensland Health
   1. In public interest
   2. Protect privacy
   3. Ethics approval
4. Hospital and Health Boards Act
5. Signed off by the chief executive

Linkage process

SSB (Data Custodian) provides the Data Linkage Unit (linkage staff) with (an encrypted) source Record Number and demographic details for each patient record in the different datasets; ***no clinical variables are included***

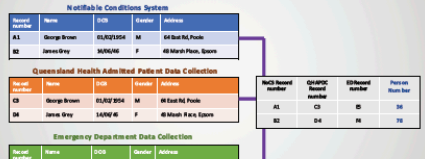


Linkage Process

- Data Linkage Unit **links** these different records using **probabilistic matching** of the demographic details
- Data Linkage Unit assigns a **Person Number** for records that belong to that person

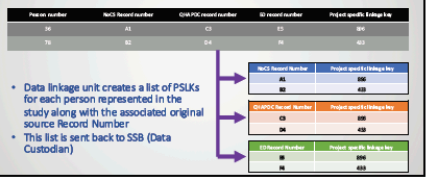
(deterministic matching uses unique identifiers, e.g. Medicare numbers)

Linkage Process

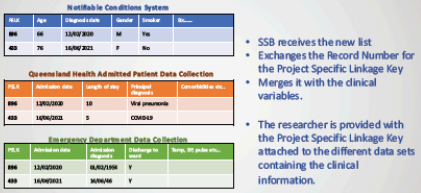


Linkage Process

For the specific project approved, the Data Linkage Unit assigns a Project-Specific Linkage Key (PSLK) for each person in the linked data set



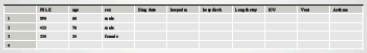
- Data linkage unit creates a list of PSLKs for each person represented in the study along with the associated original source Record Number
- This list is sent back to SSB (Data Custodian)



- SSB receives the new list
- Exchanges the Record Number for the Project Specific Linkage Key
- Merges it with the clinical variables.
- The researcher is provided with the Project Specific Linkage Key attached to the different data sets containing the clinical information.

Linkage Process

The researcher (at ANU) is then able to combine the records for the same person from the different datasets using the PSLK



Linkage Process

This record linkage process ensures:

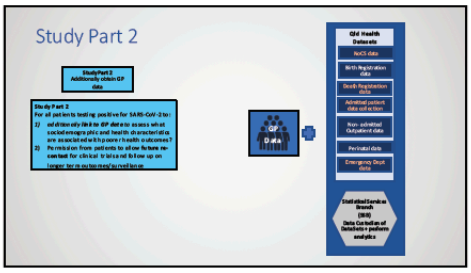
- Data linkage staff performing the linkage use demographic variables but do not have access to the clinical information about the individuals
- Data Custodians only have access to data within their data collections; and
- Researchers receive data that contains no identifying variables.

The Separation Principle
no one working with the data can view both the linking (identifying) information (such as name, address, date of birth) together with the merged analysis (content) data (such as clinical information) in an integrated dataset.

"The ATHENA COVID-19 Study: Cohort profile and first findings for people diagnosed with COVID-19 in Queensland 1 January to 31 December 2020"

(Accepted for publication Communicable Diseases Intelligence)

Study Part 2



Study Part 2

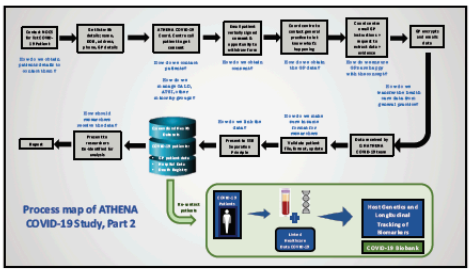
- Additional GP data
- Do we need individual patient consent?
  - Extracting identifiable patient information
  - Use for research
  - Use for re-contact
  - Privacy Act 1988

Privacy Act 1988

No. 119, 1988 as amended

Compilation start date: 12 March 2014

Includes amendments up to: Act No. 13, 2013



Questions?