Health Risk Factors Associated with Morbidity and Mortality in a National Sample of

People with Psychosis

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THESIS ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in people with psychosis. For over a decade, extensive research has shown that people who have a psychotic illness are more likely to live an unhealthy lifestyle and engage in health risk behaviours compared with the general population. The current thesis extends this prior research, using the World Health Organisation (WHO) as a framework to identify risk factors that are responsible for morbidity and mortality among the psychosis population. Out of the eleven health risk factors outlined by WHO, the first three manuscripts focus on two of these risk factors while the remaining manuscripts draw eight risk factors together to provide an overall picture of the health profile in people with psychosis.

This research was based on the 2010 Australian national psychosis survey using a large representative sample of adults aged 18-64 years with psychotic disorders ($n =1825$). The first aim of the thesis was to identify factors associated with individual WHO risk factors in people with psychosis. Paper 1 explored factors associated with dietary inadequacy defined by the consumption of less than four daily servings of fruit and vegetables. Quantitative findings derived from this paper indicated that almost three quarters of participants failed to conform to dietary guidelines, and substance use was the major contributing factor for this dietary non-compliance. Paper 2 extended these findings by providing a comparison of nutrient intake in individuals with psychosis and the general population based on a smaller subset of this population. The former group consumed more fat, vitamins and minerals compared with the normal population. Most people with psychosis did not meet the recommended dietary intake for various nutrients. Paper 3 undertook an investigation into arterial stiffness and peripheral resistance and found that male gender, higher age and a family history of hypertension was positively associated with both of these blood pressure components. In this paper, unmodifiable risk factors were more related with increasing pulse pressure and mean arterial pressure, compared with modifiable risk factors relating to poor health behaviours.

The second aim of this thesis was to investigate the absolute number of the WHO-defined risk factors, present in people with psychosis. A risk factor count represents a novel approach to obtaining an overall picture of risks that are associated with disability and death. Paper 4 looked at the total number of these CV risks present in people with psychosis, with a particular focus on young people aged 18-24 years. This paper showed that young men and women had an average of 2-3 risk factors out of 8 WHO-defined risk factors. Paper 5

expanded these findings by examining the total number of CV risks in people with psychosis aged 18-64 years. Relative to the younger participants, older people with psychosis had more risk factors, and risk appeared to increase with increasing age.

Taken together, these findings presented within the following chapters, heighten our understanding of the physical health profile and excess mortality in people with psychosis, using risk factors well-validated by the WHO, that make a substantial contribution to morbidity and mortality.

DECLARATION

I, Lisa Hahn, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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PUBLISHED WORKS

Chapter 3: Paper 1

Hahn, L. A., Galletly, C. A., Foley, D. L., Mackinnon, A., Watts, G. F., Castle, D. J., Watterreus, A., & Morgan, V. A. (published). Inadequate fruit and vegetable intake in people with psychosis. *Australian & New Zealand Journal of Psychiatry:* 48(11):1025-35.

Chapter 4: Paper 2

Nenke M. A., **Hahn, L. A.,** Thompson C. H., Liu, D., & Galletly C. A. (published). Psychosis and cardiovascular disease: Is diet the missing link? *Schizophrenia Research*: 161(2-3): 465-70.

UNPUBLISHED WORKS

Chapter 5: Paper 3

Hahn, L. A., Mackinnon, A., Foley, D. L., Morgan, V. A., Waterreus, A., Watts, G. F., Castle, D. J., Liu, D., & Galletly, C. A. (submitted). The role of arterial elasticity and cardiovascular peripheral resistance as clinically relevant indices of health status in people with psychosis.

Chapter 6: Paper 4

Hahn, L. A., Mackinnon, A., Foley, D. L., Morgan, V. A., Waterreus, A., Watts, G. F., Castle, D. J., Liu, D., & Galletly, C. A. (submitted). Counting up the risks – how common are risk factors for morbidity and mortality in young people with psychosis?

Chapter 7: Paper 5

Hahn, L. A., Mackinnon, A., Foley, D. L., Morgan, V. A., Waterreus, A., Watts, G. F., Castle, D. J., Liu, D., & Galletly, C. A. (submitted). Risk factors for death and disability in psychosis – the total picture?

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CHAPTER 1: Overview and Literature Review

The current thesis explores various health risk factors that contribute to cardiovascular disease (CVD) among people diagnosed with a psychotic illness. Risk factors were selected from the World Health Organisation (WHO) as they represent the leading causes of morbidity and mortality around the world and are highly relevant to people with psychosis. The selected risk factors were important to explore in individuals with psychosis, because they die prematurely compared with the general population. Therefore, understanding the determinants of poor health could help reduce the burden of disease and mortality among this population. This research project included two distinct research aims that have been presented in five papers, all of which have been either published or submitted to peer-reviewed journals. This thesis is focussed on these five research papers which have been presented in chapters' three to seven in their publication or submitted format.

Throughout this thesis, comparisons made to people with psychosis are based on general population data and not with other marginalised groups that may also reflect socio-economic deprivation (i.e. aboriginal people or homeless people). While other minority groups may share similar circumstances and behaviours to people with psychosis, such as, unemployment, lower income, substance use, physical inactivity and lack of a nutritional diet, the focus throughout this thesis is on people with psychosis as they need specialised interventions tailored around the outcomes of having a psychotic illness. People with psychosis have varying comorbid physical and mental health conditions, reflecting a neglected but very important population in our society that are highly deserving of intervention.

Chapter One, the current chapter, provides an overview of the individual risk factors outlined by the WHO and their current definitions. This chapter also lists the number of deaths and DALYS (disability adjusted life years) that are attributed to each health risk factor and illustrates the main risk factors that cause ischemic heart disease. The WHO has identified 8 risk factors that are specifically associated with CV disease. A summary of the research literature on these eight WHO-defined risk factors in people with psychosis will be undertaken to provide an overview of the poor health behaviours in individuals that ultimately have an effect on CV illness. This chapter will include a comparison of the prevalence of CVD in people with psychosis and in the general population to underpin the importance of addressing these risks among people with psychosis. Associations of each risk factor will be examined among this population to provide a broader context of how these risks emerge. Importantly, a review of intervention services will be undertaken to examine the efficacy of

services on CV risks. Lastly, this chapter will conclude with a brief overview of what the current literature has highlighted concerning the eight WHO-defined risk factors to provide a depiction of their overall physical health and other factors that may compound their state of health.

Chapter Two incorporates an exegesis for each of the five manuscripts. The opening of this chapter begins with a discussion on why it is necessary to investigate the WHO-defined risk factors in people with psychosis. An overview of the research project from where the data was obtained is provided to place this current research in context.

Chapters Three to Seven incorporate the five manuscripts and are divided into two sections. The first section, section A titled "Individual Risk Factors for Cardiovascular Disease" and section B titled "Total Number of Risk Factors Present", correspond to the two research aims that have been previously described. The manuscripts in this thesis have been inserted in their published or submitted format.

Chapter eight represents a general conclusion, summarising the overall significance of the five manuscripts, and the contributions this work has made to the field of knowledge in the research area. Finally, this chapter will acknowledge any methodological limitations of this research thesis, and review future directions of this work.

The World Health Organisation (WHO): Risk Factors and their Current Definitions

The purpose of this section is to review the health risk factors in the 2009 Report 'Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks', Published by the World Health Organisation (WHO). This report was used as a framework for this thesis, to determine the risk factors to be explored among people who have a psychotic illness. To date, research relating to the WHO-defined risk factors in people with psychosis, has been reviewed by Wildgust and Beary (2010). However, the current thesis aimed to provide an extension to these findings in terms of risk factor prevalence among people with psychosis compared with the general population; and report on the possible associations of these risks that may provide a broader context of the health risk profile among people with psychosis. Importantly, the risk factors examined by the WHO, may support the excess mortality that is more pronounced in individuals with severe mental illness compared with the normal community.

The WHO has identified eleven leading global risk factors in high income countries that are responsible for the development of chronic diseases including heart diseases and

cancer. However, this thesis focuses on eight of these risk factors as they are specifically associated with CVD and is the leading cause of death in people with psychosis. The eight risk factors are alcohol use, tobacco use, high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake and physical inactivity. Together, these risks account for 61% of disease burden from cardiovascular disease (CVD) and 61% of cardiovascular (CV) deaths. The population percentage of DALYS and deaths related to each of the risks is listed in Table 1. The population percentage and DALYS has been measured by determining the proportion reduction in population disease or mortality that would occur if this risk was reduced to an ideal level. For example, if no one consumed alcohol, the death rate would fall by 1.6% and the degree of disability would decline by 6.7%. Based on Table 1, tobacco use and alcohol use are the leading causes of disease burden; while tobacco use and high blood pressure are the leading causes of mortality. Due to the high rates of unemployment and low rates of narcotic use among this sample of people with psychosis, occupational risks and illicit drug use was not examined in this current thesis. In addition, the eight risk factors are also illustrated in figure 1, in order to show the interaction of these risk factors in causing ischemic heart disease. Risk factors such as high blood pressure, high cholesterol and Type 2 diabetes, act as a direct cause of heart disease, while factors located further back in the chain including, physical activity, fat intake, overweight, alcohol and smoking, act as secondary causes of the disease. The importance of the eight risk factors is that they are modifiable and can potentially be reversed to slow down or prevent CV illness.

Table 1. Percentage of DALYs[*] and Deaths for each WHO risk factor in high income countries – general population

Risk factor	DALYs (%)	Deaths (%)
Tobacco use	10.7%	17.9%
High blood pressure	6.1%	16.8%
Overweight and obesity	6.5%	8.4%
Physical inactivity	4.1%	7.7%
High blood glucose	4.9%	7.0%
High cholesterol	3.4%	5.8%
Low fruit and vegetable intake	1.3%	2.5%
Urban outdoor air pollution	-	2.5%
Alcohol use	6.7%	1.6%
Occupational risks	1.5%	1.1%
Illicit drugs (cocaine, heroin and amphetamines)	-	2.1%

*DALY = disability- adjusted life year. One DALY = one lost year of 'healthy' life. (WHO, 2009)

Figure 1: The causal chain. Major causes of ischaemic heart disease are shown. Arrows indicate some (but not all) of the pathways by which these causes interact.
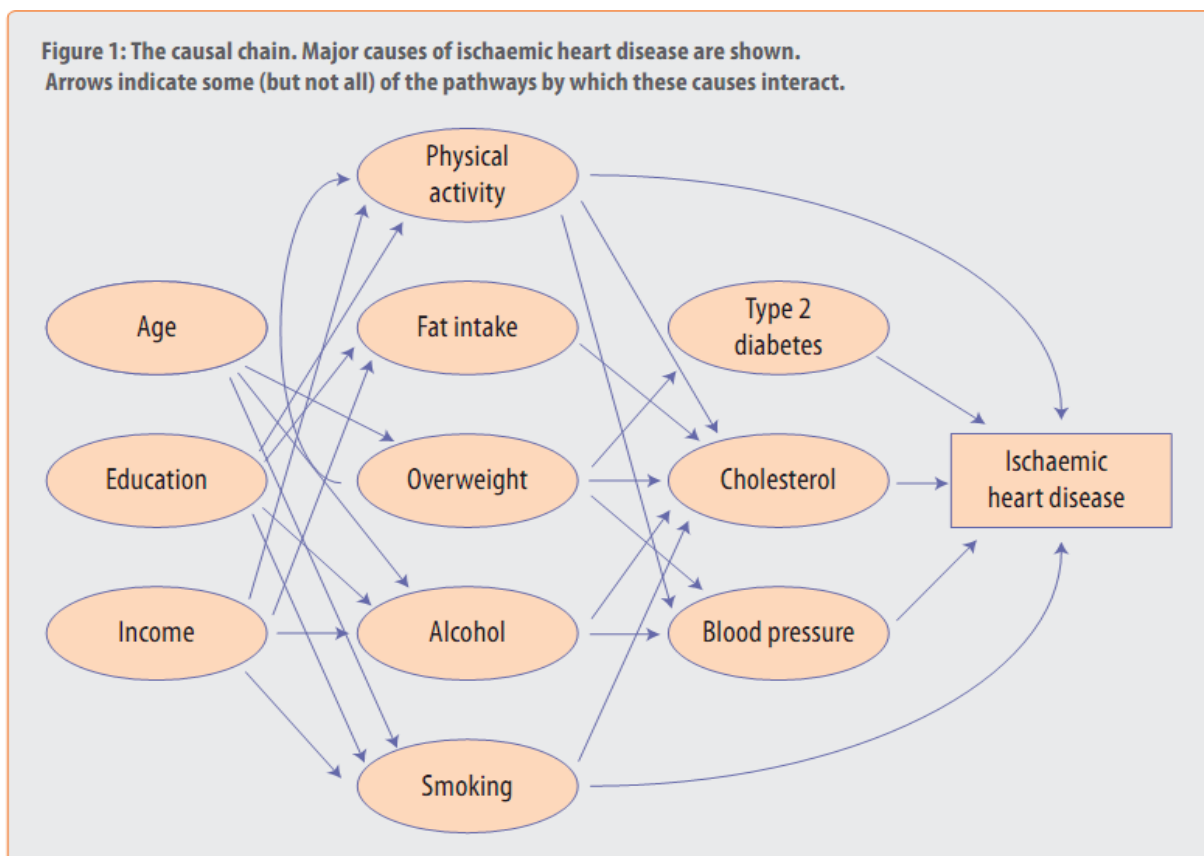
Figure 1. WHO (2009).

Table 2. Risk factor definitions from the 2009 Global Health Risks Report.

Risk factor	WHO definition
Tobacco use	Current smoker
High blood pressure	Systolic ≥ 140 mmHg
Overweight and obesity	BMI ≥ 25
Physical inactivity	< 2.5 hour per week of moderate intensity activity or < 1 hour per week of vigorous activity (equivalent to 600 MET minutes)
High blood glucose	≥ 5.6 mmol/l
High cholesterol	≥ 6 mmol/l
Low fruit and vegetable intake	< 5 servings of fruit and vegetables/ day
Alcohol use	≥ 40 grams alcohol/day (≥ 4 standard drinks)

Literature Review of WHO Risk Factors

Tobacco Use

Tobacco use is the primary risk factor for death and disability in developed countries around the world and presents a major risk factor for cardiovascular disease. Over 4000 chemicals are contained in cigarettes and the mechanisms by which these substances negatively affect cardiovascular health have been well established. Smoking increases the progression of atherosclerosis whereby the build-up of plaque narrows the arteries, restricting the flow of oxygen-rich blood to vital organs and other parts of the body (Brunner et al., 2005). Ultimately, this increases the risk of a heart attack, stroke or death. Another mechanism facilitating the development of atherosclerosis is 'thrombosis', involving the activation of platelets that can lead to blood clotting and damage to the lining of the arteries (Brunner et al., 2005). Smoking also causes an increase in total cholesterol, triglycerides and low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL-C), also known as the 'good cholesterol' (He et al., 2013). Free oxygen radicals, also known as 'toxins' that are derivatives from cigarettes, increase oxidative stress, therefore, anti-oxidants that would regularly protect the body against free radicals become depleted (Yanbaeva et al., 2007).

While there has been a decrease in national smoking prevalence in Australia over the past decade in adults aged 18 years and over (25.4% of men and 19.5% of women in 2001; 18.3% of men and 14.1% of women in 2011-2012) (Australian Bureau of Statistics, 2013b), smoking prevalence in people with psychosis has remained relatively unchanged. In Australia, between the years 1997-1998, 76.1% of men and 57.6% of women with psychosis were current smokers, and this has remained moderately stable over the following 15 years. In 2010: 72.2% men and 59.7% of women with psychosis were current smokers (Morgan et al., 2012). It has previously been estimated that 80-90% of people with schizophrenia are smokers (Chapman et al., 2009). The trajectory of current smoking among people with schizophrenia in international studies has not been that different to Australian studies, ranging between 50-75% from 2001-2011 (Dickerson et al., 2013). This suggests that the introduction of tobacco-control campaigns have clearly been effective in targeting smoking in the general community, but unfortunately, this does not appear to be the case for people with psychosis.

A number of explanations have previously been considered for the persistent high rates of cigarette smoking in people with psychosis. Generally, tobacco smoking in the wider

population has been linked to socioeconomic disadvantage, characterised by poorer neighbourhood residence, lower education, lower income, lower occupational status and unemployment (Lawrence et al., 2013). In light of this, people with psychosis are more likely to be disadvantaged on all of the above socioeconomic indicators (Hahn et al., 2014a) (see Appendix A) and represent one of society's marginalised groups in terms of facing numerous barriers to access of health care. Nicotine addiction is costly; therefore, many people with psychosis endure increased financial hardship, leading them to go without basic necessities such as adequate food and clothing. Due to high unemployment rates and more than three quarters of people receiving a government pension (87.4%) (Morgan et al., 2012), the cost of supporting nicotine addiction presents a great financial burden to the psychosis community.

Smoking, to some extent, has been addressed by health professionals. In a recent systematic review and meta-analysis by Mitchell et al (2015), the rates of smoking cessation advice received by people with severe mental illness and people in the general population attending primary and secondary care settings were, comparable. This remains a concern, as people with psychosis have a much higher prevalence of smoking compared with the general population, therefore, it would make sense if this population received more assistance regarding their smoking behaviour. Individuals with severe mental illness are reported to have limited access to tobacco cessation treatment services and health services, thus, delivering such services in a more convenient way may be effective in addressing and targeting tobacco smoking behaviour.

The strong connection between smoking and psychosis suggests a shared genetic vulnerability for tobacco use. People with schizophrenia tend to smoke more cigarettes per day and inhale the tobacco smoke more deeply compared with smokers in the general population (Rohde et al., 2003; de Leon and Diaz, 2005). For a long time, researchers have attempted to establish a shared genetic component that may explain tobacco dependence in schizophrenia. This has particularly gained interest due to the notable high smoking rates that already exist prior to the diagnosis of schizophrenia (de Leon and Diaz, 2005). A history of evidence gathered over the years, has identified polymorphisms linked to the α7 nicotinic acetylcholine receptor (nAChR) gene in individuals with schizophrenia (Leonard et al., 1996; Freedman et al., 1997; Stassen et al., 2000; Stephens et al., 2009; Mexal et al., 2010). Studies have found abnormalities in the expression of these receptors in individuals with schizophrenia; findings have previously revealed a reduction of α7 nAChR function as a latent mechanism for increased tobacco use in schizophrenia that may have important implications for addressing tobacco cessation therapy (Brunzell and McIntosh, 2012). In addition, there is supporting evidence that nicotine addiction may be heritable among first

degree relatives of individuals with schizophrenia: 44.9% of unaffected first degree relatives of people with schizophrenia were current smokers compared to 23.6% healthy controls (Ferchiou et al., 2012) suggesting that the relatives of schizophrenia patients may be genetically pre-disposed to becoming cigarette smokers. Emerging research is beginning to support the idea that smoking may be implicated in the risk of developing psychosis (Myles et al., 2012). For example, individuals who were daily, heavy tobacco users before the age of 15 years were likely to have delusion-like experiences following their tobacco use (Saha et al., 2011). Further supporting evidence has shown smoking to be associated with psychotic-like experiences and non-affective psychosis over and above cannabis use (van Gastel et al., 2013; Gage et al., 2014; McGrath et al., 2015). Taken together, this suggests that tobacco may be fundamentally implicated in the genetic mechanisms of psychosis.

The self-medication hypothesis has traditionally been used in support of the excess smoking in people with psychosis. Edward Khantzian, first introduced this theory in the mid 1980's with an original focus on heroin and cocaine dependence, suggesting that drugs of choice by addicts are not random, but rather methodical as their "choice is the result of an interaction between the psychopharmacologic action of the drug and the dominant painful feelings with which they struggle" (Khantzian, 1985). Self-medication theories relating to tobacco use in psychosis suggest that individuals with schizophrenia smoke excessively due to the alleviation effects of nicotine on psychotic symptoms or side-effects from antipsychotic therapy. In particular, nicotine administration is believed to play a therapeutic role in reducing cognitive deficits in schizophrenia relating to attention and working memory (Olincy and Freedman, 2012). Examples of improvements have been shown in visual spatial memory, speed of finger tapping, sensory auditory gating and smooth-pursuit eye movements (McEvoy and Allen, 2002; Silver et al., 2002). However, some authors propose there have been methodological issues with these findings. Ragg and Ahmed (2008) suggest these findings have been limited by people who smoke regularly, which make it difficult to determine if any improvement is caused by the effects of nicotine per se or whether any improvement is caused by nicotine withdrawal whilst completing the task. Performance tasks are conducted among smokers with nicotine addiction, and findings are often recorded before and after the person has had a cigarette. Results of the performance task may be confounded by nicotine withdrawal, therefore, comparing task performance among non-smokers before and after the person has a cigarette may provide more accurate information. Less clinical data has been gathered regarding nicotine administration and outcomes of performance tasks, as research studies are generally conducted in laboratory settings (Ragg and Ahmed, 2008). Taken together, excessive smoking in the psychosis population may not be fully explained by the

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self-medication hypothesis, and may be more linked to other factors such as nicotine addiction and boredom (Peckham et al., 2015; de Leon and Diaz, 2005). It appears nicotine may be less beneficial on psychiatric symptomatology than previously thought.

Research suggests that chemicals found in tobacco smoke may interact with antipsychotic medication. Smoking induces the activity of human cytochromes P450 (CYP) 1A2 and 2B6 (Hukkanen, 2012) resulting in the metabolism of clozapine and olanzapine, thereby, lowering plasma concentrations (Tsuda et al., 2014; Dobrinas et al., 2011). Smoking cessation can be especially dangerous among people treated with antipsychotics medication. Kennedy et al (2013) reports on the influences of smoking on second-generation antipsychotics in his review article. Plasma clozapine concentrations showed a mean increase of 72% when smoking was ceased due to the slower clearance of clozapine in the blood (Kennedy et al., 2013). Furthermore, in a population based study ($n = 519$), it has been previously shown that smoking 7-12 cigarettes/day was sufficient to produce maximum enzyme induction and a significantly lower mean clozapine C/D ratio in smokers than in non-smokers (2.8 ng/mL/mg/day versus 6.0 ng/mL/mg/day) (Ng et al., 2009). In a retrospective study ($n = 48$), patients with schizophrenia, who smoked had a mean plasma clozapine concentration of 500 µ/L (Cormac et al., 2010). After the introduction of a smoke-free hospital policy in the former study, mean plasma clozapine levels increased to 900 µ/L in schizophrenia patients (Cormac et al., 2010). Surprisingly, clozapine doses were not changed during the implementation of the smoke ban and side effects from smoking cessation were experienced from the patients (i.e. convulsions and myoclonic jerks). Case reports on smoking discontinuation by patients treated with clozapine and olanzapine also report on experienced side effects including confusion, tonic-clonic seizures, stupor, coma, aspiration pneumonia and extrapyramidal symptoms (akathisia, akinesia and bradyphrenia) (Lucas and Martin, 2013). A population study (n = 523) examining the influence of smoking on olanzapine using plasma samples showed that mean olanzapine centilitre (CL) was significantly increased by 55% in smokers compared with non-smokers and this accounted for the highest level of variability (26%) compared with other factors (e.g. sex and race) (Bigos et al., 2008). Other antipsychotic medications that are metabolised by enzymes in tobacco smoke include: risperidone, aripiprazole, quetiapine and paliperidone (Lu and Lane, 2016). It is suggested that daily dose reductions of approximately 10% until the fourth day after smoking discontinuation, should be made whenever patients stop smoking during treatment, with clozapine (Lucas and Martin, 2013). In light of these findings it is important that doses of antipsychotic medication are adjusted appropriately with regard to smoking status and extent of cigarette consumption. Patients should be regularly and closely monitored by health

care professionals to prevent any adverse side-effects from smoking cessation. To understand smoking behaviour in psychosis, it must be viewed in relation to a person's environment and other comorbid substance use behaviours. While psychiatric hospitals are increasingly adopting smoke-free policies (Soyster et al., 2016) high smoking rates still persist in hospitals that are yet to implement smoking bans. More than half of inpatient psychiatric units in the United States (US) permit smoking and half of these units sell tobacco products to patients (Lane et al., 2009). This makes smoking cessation difficult, particularly when patients are influenced by the smoking behaviours of others. Around half of people with psychosis who have a lifetime diagnosis of alcohol or cannabis abuse/dependence are current smokers (Hahn et al., 2014a) (See Appendix A); and those who are current smokers are four times more likely to report abuse or dependence of other illicit drugs (Cooper et al., 2012). It has previously been suggested that alcohol dependent individuals in the general population, smoke more cigarettes per day, take more puffs per cigarette and inhale more deeply and smoke sooner upon awakening in comparison to less dependent drinkers (Bowman and Walsh, 2003). Due to the higher rates of alcohol use disorders in people with psychosis compared with the general population, it could possibly be inferred that people with psychosis that drink excessively, smoke in a way that makes them become more nicotine dependent.

People with schizophrenia are more nicotine dependent compared to smokers in the general population (de Leon and Diaz, 2005) that may explain the increased struggle with quitting smoking compared with their healthy peers. The belief that people with severe mental illness are not motivated to quit smoking, has been challenged in recent years. South Australian smoking cessation programs tailored around people with severe mental illness has shown encouraging results. Information relating to: mental health, physical health outcomes associated with smoking, dealing with boredom and stress, building confidence and coping strategies, were provided by course leaders and peer support workers during two sessions per week, over the period of 10 weeks (Ashton et al., 2010). Carbon monoxide levels were obtained throughout the course to monitor smoking behaviour and nicotine replacement therapy was provided (NRT) to assist with nicotine withdrawal. Among 581 smokers who attended at least one session and completed an evaluation at the end of the program, almost a quarter of participants (22%) reported no smoking and 48% had reduced their smoking (Ashton et al., 2015) (Ashton et al., 2013). The majority of participants (85%) considered their health as a primary reason to address their smoking. Clearly, these findings demonstrate that people with mental illness, are motivated to address their tobacco use. Studies conducted outside of Australia have also shown encouraging results but abstinence rates have fallen below South Australian estimates: approximately 12% of patients with serious mental illness

achieved smoking abstinence during a randomised control trial, either through a multi-faceted behavioural group intervention or a supportive group intervention (Bennett et al., 2015). Taken together, it appears that while smoking abstinence is feasible in populations with psychosis, the nature of the intervention is important for determining effectiveness. Continued tailored support is required for preventing relapse. Importantly, smoking behaviour appears to be a complex phenomenon among this population; addressing other factors such as unemployment and increasing access to smoking cessation services may be warranted to reduce the overall prevalence of smoking in this population.

High Cholesterol

According to the World Health Organisation (WHO), high total cholesterol accounts for 3.4% of disease burden and 5.8% of deaths due to chronic disease. High levels of low-density lipoprotein (LDL) results in the build-up of cholesterol that narrows the arteries, contributing further to the formation of plaque and restricting blood flow. Increased LDL presents the greatest risk of heart disease, while raised high-density lipoprotein cholesterol (HDL-C) reduces this risk through the transportation of excess cholesterol in the blood, to the liver where it is broken down thus aiding in the prevention of blockages (Cimmino et al., 2015). Moreover, total blood cholesterol is a measure of HDL, LDL and triglycerides in the blood stream.

Women with psychosis are more likely to have high total cholesterol compared to men with psychosis (34% versus 29%) respectively; overall 31% of the psychosis population have high cholesterol (Galletly et al., 2012) and this falls slightly below national levels (32.8%) (Australian Bureau of Statistics, 2013a). Research conducted in the US also found comparable rates of high cholesterol between white people with severe mental illness (62%) and white people in the general population (62%) (Keenan et al., 2013), however this remains almost doubled in comparison to estimates derived from the Australian population and may be a reflection of the increased availability and portion sizes of fast food in the American culture. The similar prevalence of high cholesterol between both populations appears counterintuitive when viewed in light of the poorer health status (obesity, smoking, hypertension, and diabetes) among people with psychosis compared with their non-psychosis counterparts (Scott and Happell, 2011). A possible explanation for the comparable cholesterol prevalence in individuals with psychosis and the general population may be due to the lack of age and gender standardisation. A cross sectional study exploring the lipid profile in individuals with schizophrenia compared with individuals from the 2005-2008 National Health and Nutrition Examination Survey (NHANES), found that the latter group had significantly higher total

cholesterol levels and LDL-C levels (Ratliff et al., 2012). The authors concluded that this discrepancy may in part be attributed to the increased number of schizophrenia patients already receiving treatment for obesity-related comorbidities.

Despite this, low levels of HDL-C appear to be most common in people with psychosis representing approximately half of the population (49.6%) (Galletly et al., 2012) in comparison to almost a quarter of the general community (23%) (Australian Bureau of Statistics, 2013a).

The major contributing factors for raised cholesterol in the general population are poor dietary intake and familial hypercholesterolemia (Li et al., 2015; Benn et al., 2012). Data from several studies have identified that a diet high in saturated fat is one of the risk factors for raising LDL and total cholesterol (Kelly, 2010); while replacing saturated fats with poly-unsaturated fatty acids (PUFAs) or high quality carbohydrates can reduce the risk of coronary heart disease (Li et al., 2015). A systematic review conducted by Dispasquale and colleagues (2013) who examined the dietary patterns of patients with schizophrenia, concluded that their dietary intake primarily included a high consumption of saturated fat and a low consumption of fibre and fruit (Dipasquale et al., 2013), all of which contribute further to their high prevalence of overweight (29%) and obesity (46%) (Galletly et al., 2012). In addition, studies have confirmed that smokers with psychosis compared to non-smokers with psychosis, display a worse dietary intake as they are more likely to consume more alcohol, caffeine, salt, saturated fats and are less likely to follow a low caloric diet, all of which are factors that contribute to the development of heart disease (Bobes et al., 2010). More than half of the psychosis population are current smokers (49- 67%) (de Leon and Diaz, 2005; Jackson et al., 2015), and individuals who smoke are at greater risk of developing high cholesterol.

Apart from poor dietary intake accounting for elevated cholesterol, there is also with the impact of antipsychotic therapy in producing unwanted metabolic side-effects. For over a decade, some antipsychotic medications, including olanzapine and clozapine, have been shown to significantly increase mean cholesterol levels, in comparison to risperidone and haloperidol (Lindenmayer et al., 2003). A meta-analysis by Mitchelle et al (2013) examining metabolic abnormalities in first episode psychosis (FEP) patients, untreated and treated patients with schizophrenia, revealed that 41% of treated individuals with chronic schizophrenia had abnormal triglyceride levels compared with 17% of unmedicated individuals (Mitchell et al., 2013a). This suggests that individuals with psychosis, who take anti-psychotic medications over time, are at greater risk of developing lipid abnormalities than their medication naïve counterparts. In support of this, reduced HDL-C levels among

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patients with schizophrenia have been associated with longer duration of illness (De Hert et al., 2006), which may reflect the effect of anti-psychotic medication on the occurrence of metabolic issues.

The development of excess total cholesterol or LDL-C and lowered HDL-C in the blood, is directly related to smoking, alcohol intake, high body mass index (BMI) and physical inactivity (WHO, 2009). Therefore, it would be practical to address these factors to decrease cholesterol levels. Interventions addressing cholesterol levels in people with psychosis have primarily targeted weight (McGinty et al., 2015). A recent study by Green et al (2015), investigated a lifestyle intervention using a randomised trial in people with severe mental illness. The authors of this study assessed outcomes associated with weight and diabetes risk among people who were taking antipsychotic medication ($n = 104$). The intervention consisted of a series of weekly 2 hour group meetings, including 20 minutes of moderate physical activity delivered over a 6 month period. Participants were educated on the benefits of eating a healthy diet and exercising regularly and information was recorded to assess any progress. The study found that the intervention participants lost 4.4 kilos more than participants in the control group from baseline to 6 months; however in the intervention group, no significant reductions were found from pre- to post-intervention regarding triglycerides, LDL-C or HDL-C (Green et al., 2015b). Similarly, a meta-Analysis exploring the effects of lifestyle interventions on weight management and cardiometabolic risk in people with psychotic disorders, found no significant differences between the type of intervention administered (weight loss interventions and weight gain prevention interventions) for total cholesterol, HDL-C and LDL-C; however, lifestyle interventions (consisting of a nutritional element, physical activity and/or psychological intervention aimed at weight loss or weight gain prevention) had a small to moderate, significant effect on triglycerides (Bruins et al., 2014). This suggests that different interventions may be required for targeting different types of lipids.

High Blood Glucose

High blood glucose ranks as the fifth global health risk factor accounting for death and burden of disease (WHO, 2009). Glucose is a primary source of energy supply for the human body. People with high blood glucose levels (also known as hyperglycaemia) or diabetes have a lack of production of the hormone insulin, which is vital for the conversion of glucose (sugar) into energy and the absorption and transportation of sugar from the blood stream. Consequently, glucose that is consumed in certain food products remains in the blood instead of being converted into energy, hence, resulting in high levels of glucose in the blood stream.

Ultimately, over time, this can damage nerves and blood vessels leading to complications such as heart disease and stroke (Patel et al., 2015). Different types of diabetes exist. Type 2 diabetes mellitus is a progressive and chronic condition where the body becomes resistant to the normal effects of insulin or gradually loses the capacity to manufacture enough insulin in the pancreas. On the other hand, Type 1 diabetes mellitus is an auto-immune condition where the immune system mistakenly attacks the insulin producing hormone resulting in little or no insulin production (Atkinson et al., 2014). It has previously been assumed that Type 1 diabetes occurs in childhood and Type 2 diabetes occurs in adulthood and while this is true, recent research has shown that Type 1 diabetes also exists among adolescents and young adults due to the increased rates of obesity (American Diabetes Association, 2015).

Approximately 11% of people with schizophrenia and related psychotic disorders have diabetes (Mitchell et al., 2013b), which exceeds diabetes rates in the Australian population (5.1%) (Australian Bureau of Statistics, 2013a). In addition, it has been recognised for a long time that individuals with schizophrenia have a higher prevalence of glucose metabolism abnormalities, insulin resistance and type 2 diabetes compared with the general population (Henderson et al., 2005; Kohen, 2004). Relative risk estimates reveal that people with schizophrenia are 2.5 times at increased risk of developing diabetes compared with the general population (Stubbs et al., 2015). Approximately 1 in 5 people with schizophrenia have diabetes or hyperglycaemia (Mitchell et al., 2013b) and this is usually more common in women compared to men (22.4% versus 19.8%) (Galletly et al., 2012). The risk of death in people with psychosis is increased following the diagnosis of Type 2 diabetes. For example, 15% of people with schizophrenia below the age of 50 years died within 7 years of receiving a diagnosis of Type 2 diabetes (Ribe et al., 2014).

Predictors of Type 2 diabetes in people with psychosis have previously been linked with obesity (Foley et al., 2014), primarily through excess weight interfering with the body's ability to maintain suitable blood glucose levels, increasing the risk of insulin resistance (Henderson et al., 2015). In further support of this, 48% of obese people with schizophrenia have diabetes in contrast to 15% of obese controls (without schizophrenia) (Ratliff et al., 2013). Among the general population, research has demonstrated that a body mass index (BMI) of at least 40 is linked with a 7-fold increased risk of diabetes, while in men and women with psychosis a BMI of at least 40 is associated with a 9 fold increased risk and 14-fold increased risk of diabetes, respectively (Mokdad et al., 2003). It is well known that people with psychosis also consume a poorer diet in comparison to the general community (Dipasquale et al., 2013) further contributing to their excess weight and impaired glucose metabolism.

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Laboratory findings reveal that the co-occurrence of schizophrenia and Type 2 diabetes may be the result of shared genetic risk variants (Zhang et al., 2013), indicating that this population may already be predisposed to developing diabetes. Previous research has shown that the risk of Type 2 diabetes was significantly increased in association with family history of diabetes after adjustment for age and gender and all other predictors (Foley et al., 2014), again suggesting that genetic risk variants may be related to the observed comorbidity between Type 2 diabetes and schizophrenia. Further studies reveal that individuals with psychosis who do not have a family history of diabetes but are taking antipsychotic medication are at increased risk of diabetes mellitus (Foley et al., 2015b). The prevalence of glucose metabolism abnormalities is higher in patients receiving second-generation antipsychotics than in patient's receiving first generation antipsychotics (Sikich et al., 2008). A five-year naturalistic study exploring the effects of the antipsychotic drug clozapine on a range of metabolic indices, found that during the 5- year follow-up, approximately 37% of individuals were diagnosed with diabetes (Henderson et al., 2000). The association between clozapine and Type 2 diabetes has also been confirmed by Foley et al (2014), and the association between olanzapine and Type 2 diabetes has been supported by Yood et al (2009), suggesting that antipsychotic agents may increase the progression of this disease, particularly clozapine and olanzapine bearing a significantly higher burden.

Previous work has established that patients with schizophrenia and comorbid diabetes were significantly more likely to have poor adherence to their hypoglycaemic medications compared with their anti-psychotic medications (Piette et al., 2007). This may in part explain why almost 40% of the psychosis population have diabetes or hyperglycaemia despite being prescribed medication to treat this condition (Galletly et al., 2012). A recent review of the literature in the general population exploring the comorbid relationship between diabetes and stress found that stress-related factors were indeed linked with Type 2 diabetes independent of behavioural and traditional risk factors (Kelly and Ismail, 2015). Furthermore, prospective findings from this study suggest that the activation of the physiological stress response from chronic exposure to stressors including low-socio economic status (currently or in early childhood), traumatic events, aggressive behaviour and conflict with others, increases the risk of Type 2 diabetes (Kelly and Ismail, 2015). It is well known that people with psychosis have a lower-socioeconomic status and are more socially disadvantaged compared with the general population. This has been reflected by crime and neighbourhood disorganisation (Veling et al., 2015), unemployment, lower education and poor physical health (Sweeney et al., 2015). In support of this, Tsai et al (2014) reported that people with schizophrenia with low individual socio-economic status (defined by occupation and education) living in

disadvantaged neighbourhoods had a 18-22% increased risk of mortality, compared to individuals with high individual socio-economic status living in advantaged neighbourhoods (Tsai et al., 2014). Taken together, these findings indicate that environmental stressors determined by low-socioeconomic standing and residence in disadvantaged neighbourhoods have a detrimental effect on health and in particular the development of Type 2 diabetes.

Research shows that metabolic screening in the detection of cardiovascular disease is conducted more regularly in people in the general population who have diabetes compared with people who have psychosis. Hardy and Colleagues (2013) found that only 35% of people with severe mental illness received screening for high blood glucose levels in primary care practice (Hardy et al., 2013). Regarding lifestyle advice and screening administered by general practitioners, only 8% of people with severe mental illness received a full cardiovascular disease (CVD) screen in conjunction with lifestyle guidance relating to blood glucose, blood pressure, cholesterol, smoking, BMI, diet and exercise (Hardy et al., 2013). This disparity in health care at the primary service level, suggests there exists a lack of awareness of the need for screening, health promotion and prevention advice for people with severe mental illness among general practitioners. Routine screening is warranted so that metabolic issues can be detected early to prevent their full progression.

In the general community, strong research evidence shows that higher levels of sedentary behaviour are associated with over a 2-fold increased risk of Type 2 diabetes and cardiovascular disease (Wilmot et al., 2012). Individuals with schizophrenia are known to be more sedentary and physically inactive compared with the general community (Soundy et al., 2013), suggesting that this population are at even greater risk of developing diabetes. While physical exercise is beneficial in decreasing weight and lowering blood glucose levels, it also increases insulin sensitivity, and stimulates other mechanisms in the body to promote the uptake of glucose and use it for energy whether insulin is or not available (Sigal et al., 2013). A systematic review of diabetes self-management interventions for people with schizophrenia or schizoaffective disorder showed that addressing diet and exercise behaviours can be effective in managing Type 2 diabetes; however, the authors also highlighted that factors including decreased cognition, limited resources, amotivation and increased weight due to antipsychotic side effects, pose significant challenges, suggesting that such interventions must be tailored around the individual needs of the patient (Cimo et al., 2012).

Alcohol use

According to the WHO, alcohol consumption is the second leading risk factor in high income countries accounting for 6.7% of cardiovascular related morbidity. The contribution of

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alcohol towards death, however, is lower (1.6%) (WHO, 2009). A review exploring the effect of alcohol on cardiovascular health revealed that excessive drinking can have toxic and harmful health effects on the body due to the active ingredient, ethanol, leading to chronic disease of the heart muscle (cardiomyopathy), high blood pressure, ischemic stroke, diabetes mellitus and an increase in low-density lipoprotein (LDL) cholesterol. (O'Keefe et al., 2014). Conversely, growing research has shown that light to moderate alcohol intake measured by 1-2 drinks per day, can provide beneficial health effects, such as, improving insulin sensitivity, increasing high-density lipoprotein (HDL) (good cholesterol), decreasing triglycerides, reducing inflammation, increasing adiponectin (a protein implicated in the regulation of glucose levels and fatty acid breakdown) improving endothelial function and decreasing abdominal obesity (Krenz and Korthuis, 2012; Perissinotto et al., 2010; Wakabayashi, 2010). Despite this, high alcohol intake presents a major risk factor for cardiovascular related morbidity and poses a significant risk to society due to its ease of availability and social acceptability. Current national guidelines suggest drinking no more than two standard drinks on any day reduces the risk of harm from alcohol-related disease or injury over a lifetime and; drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion (National Health and Medical Research Council, 2009).

Approximately 20% of Australian adults exceed the lifetime risk alcohol guidelines and approximately 45% of Australian adults exceed the single occasion risk guidelines (ABS, 2012). To date, estimates of lifetime risk and single occasion risk of alcohol use have not yet been reported separately in people with psychosis. Instead, a recent study, examining health risk behaviours in people with mental illness, measured alcohol risk by identifying people who exceeded both the lifetime risk and single occasion risk of alcohol consumption; the authors found that approximately 43% of people with schizophrenia and bipolar disorder consumed more than two standard drinks on any drinking day or consumed more than four standard drinks on a single occasion (Bartlem et al., 2015). Much literature has shown that people with psychosis are more likely to suffer from alcohol abuse and dependence compared with the general population. In individuals with schizophrenia, alcohol misuse has individually predicted cardiovascular related mortality (HR= 1.52) more so than cannabis (HR= 1.24) but not for hard drugs (HR= 1.78); all-cause mortality was even further increased when these substances were combined (Hjorthoj et al., 2015). These findings demonstrate that mortality in psychosis is greater among individuals with substance use disorders compared to those without substance use disorders, further compounding the excess mortality risk profile in people with psychosis.

The comorbid use of other substances in people with psychosis may explain their high incidence of alcohol use disorders. For example, alcohol consumption is higher among smokers (80.8%) compared with non-smokers (19.2%) (Bobes et al., 2010) and higher among cannabis users (82%) compared to non-cannabis users (50.5%) (Koola et al., 2012). In individuals with schizophrenia, the most consistent substances that have emerged in the literature have been: tobacco (70-90% lifetime prevalence), alcohol (30-40% lifetime prevalence) and cannabis (20-30% lifetime prevalence) (Koskinen et al., 2010; Koskinen et al., 2009; Blanchard et al., 2000). Previous studies in psychosis have established that both lifetime alcohol and cannabis dependence are significantly related to male gender and younger age (18-24 years) (Moore et al., 2012). In addition, male gender and younger age (18-34 years) have previously been linked to a poorer diet consisting of a lower daily intake of fruit and vegetables, and a higher intake of salt compared to women; people who failed to meet dietary guidelines were more also more likely to use tobacco, alcohol and cannabis, in comparison to people who adhered to dietary guidelines (Hahn et al., 2014b).

Research suggests that people with schizophrenia may use alcohol for the same reasons as people in the general population, where factors relating to sociability, pleasure and coping purposes appear to be similar motives for drinking behaviour across both groups (Thornton et al., 2012a; Lyvers et al., 2010; Hasking et al., 2011; Thornton et al., 2012b; Ministerial Council on Drug Strategy, 2006). In light of this, there are also additional factors that need to be considered to better understand the high prevalence of alcohol use in psychosis. Biological, psychological and environmental factors further contribute to this prevalence. For example, a study examining socioeconomic deprivation on rate and cause of death in people with psychosis, found that a higher incidence of alcohol and drug related deaths was more common in individuals with schizophrenia or bipolar disorder (12.2%) residing in the most deprived region compared to people without psychosis (5.1%) who were also living in the most socially deprived region (Martin et al., 2014). Problematic alcohol use among people with psychosis has been linked to unemployment, lower educational attainment, exacerbation of psychiatric symptoms (Moore et al., 2012) paternal and maternal family history, violent offending (Jones et al., 2011) and increased rates of hospitalisation (Lin et al., 2013) compared with their peers who do not have an alcohol problem. The self-medication hypothesis also plays a role in explaining the high prevalence of alcohol use; self-medicating to relieve depression and psychotic symptoms has previously been reported (Lin et al., 2013).

Interventions addressing excessive alcohol use in psychosis have been positive. A systematic review investigating psychological interventions for excessive alcohol

consumption in people with psychosis, showed that brief motivational interventions, assessment interviews and longer cognitive behaviour therapy were significantly associated with reductions in alcohol; and brief interventions (1-2 sessions) were generally as effective as longer duration psychological interventions (10 sessions) (Baker et al., 2012). Furthermore, combining both mental health and alcohol use treatments in addressing alcohol problems have been shown to be more effective opposed to approaches that address substance use and mental health separately (Drake et al., 2008). Given that alcohol is easily accessible and relatively affordable, it seems likely that abstinence or alcohol reduction among this population may be more difficult to achieve but this does not appear to be the case. While past research has indicated the effectiveness of comprehensive psychosocial treatments such as staged treatments, assertive outreach and motivational interventions in addressing alcohol use disorders in schizophrenia, there have been barriers in employing these services in routine mental health treatment settings (Drake et al., 2001). To counter this, pharmacotherapy trials have administered medications to reduce alcohol intake in people with schizophrenia; naltrexone have shown to reduce daily and weekly intake of alcohol followed by a reduction in alcohol craving and addiction severity compared with the placebo group (Batki et al., 2007). This evidence is growing and has been confirmed in other studies (Petrakis et al., 2004; Petrakis et al., 2005; Batki et al., 2009; Batki SL, 2010). A recent randomised trial by Green et al (2015) investigating long-acting injectable compared with oral risperidone in individuals with comorbid schizophrenia and alcohol use disorders (n=95), revealed that neither medication was associated with a reduction in alcohol intake over 6 months; importantly the authors suggested the need for the right pharmacotherapy to reduce alcohol consumption. This consisted of appropriate antipsychotic treatment combined with medications that have proven efficacy in the treatment of alcohol use disorders, in addition with alcohol counselling and support (Green et al., 2015a).

BMI

Overweight or obesity as measured by body mass index (BMI) is the third leading risk factor for disability and death related to cardiovascular illness and is a growing epidemic in the developed world. Total adiposity is most commonly measured by determining a person's BMI which represents an index of a person's weight relative to their height and hence, overall body fat (Australian Institute of Health and Welfare, 2004). Obesity plays a key role in influencing the development of associated risk factors that are implicated in the development of cardiovascular disease such as atherosclerosis. Research indicates that obesity can lead to hypertension, increased triglycerides, decreased HDL-C, raised LDL-C, inflammation,

diabetes and the metabolic syndrome, all of which increase the risk of premature CV morbidity and mortality (Zalesin et al., 2011). Positive associations between BMI and ischemic heart disease have previously been established. Among adults in the general population aged 45-54 years, each 5 kg/m^2 increase in BMI above 20 kg/m^2 was associated with a 36% increased risk of ischemic heart disease (IHD) hospitalisation (Joshy et al., 2014).

While the national prevalence of tobacco use has generally declined in the past twenty years (Ng et al., 2014b), the incidence of overweight and obesity has substantially increased among children and adults in the general population (Ng et al., 2014a). In 2011-12, approximately 63% of Australian adults were overweight or obese, almost coinciding with the US where two thirds of American adults were also overweight or obese. The Australian prevalence consisted of 35% overweight adults and a further 28% obese adults and this was more common in men compared to women. Conversely, estimates of overweight or obesity in the psychosis population are well above those derived from the general population. Between 45-55% of people with schizophrenia suffer from obesity and they are 1.5 -2 times more likely to be obese compared with people without schizophrenia (Henderson et al., 2015), with a tendency for women to be more overweight or obese compared with men (Gurpegui et al., 2012). This poses an even greater risk for adult-onset diabetes and cardiovascular disorders among this population (Caemmerer et al., 2012) that ultimately leads to increased disease burden and mortality.

For many years, the weight gain associated with many anti-psychotic agents has been well known (Nasrallah, 2003; Simpson et al., 2005; Alvarez-Jimenez et al., 2010). Researchers have suggested that antipsychotic medication can induce a hypometabolic state that may play an additional role in increased appetite, caloric intake and weight gain (Cuerda et al., 2011). A post hoc analysis conducted over three years among 4626 patients with schizophrenia who were receiving mono-therapy with second generation antipsychotics including; olanzapine, clozapine, risperidone, amisulpride, quetiapine, and oral and depot first generation antipsychotics, reported weight change for all antipsychotics, but the highest gain in mean weight was observed for olanzapine (4.2 kg) (Bushe et al., 2012). Importantly, the authors reported between 7-15% of patients moved into an overweight or obese category (BMI ≥ 25) (Bushe et al., 2012). In the last ten years, research has demonstrated that abdominal obesity exists in approximately one quarter (26.6%) of people who are antipsychotic naïve with defined schizophrenia or related psychosis (Mitchell et al., 2013a). This was slightly higher compared to 22% of individuals with abdominal obesity who were in their first episode of psychosis (either medicated or unmedicated) but was much lower compared to the 52.7% of medicated individuals with schizophrenia who had abdominal

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obesity, adjusting for potential confounders (Mitchell et al., 2013a). While this does suggests there is a positive relationship between duration of antipsychotic treatment and weight, the prevalence of obesity prior to the initiation of antipsychotic therapy remains concerning.

Obesity in people with psychosis has been related to poor diet. A systematic review examining 31 papers on dietary patterns in schizophrenia, has shown that the diet of this population was primarily characterised by a high intake of saturated fat and a low consumption of fibre and fruit (Dipasquale et al., 2013). Contrary to this, data from the National Health and Nutrition Examination Survey (NHANES), showed that individuals with schizophrenia and bipolar disorder consumed fewer total calories, carbohydrates and fats, but more fibre, compared to controls (Bly et al., 2014). However, the sample of people with schizophrenia and bipolar was relatively small in the former study ($n = 143$ and $n = 116$ respectively), therefore, larger sample sizes is warranted to accurately determine the relationship between diet and obesity in people with psychosis versus the general population. Furthermore, Night Eating Syndrome (NES) characterised by a delayed pattern of food intake where the majority of calories are consumed in the evening and during nocturnal awakenings (Stunkard et al., 1955), is another factor that may explain the excess weight in psychosis and represent a key contributor to the development of obesity later on in life. The estimate prevalence of NES in the general population is 1.5% (Vetrugno et al., 2006) and approximately 10% of people in the general population with this syndrome are obese (Stunkard et al., 1996). Findings by Palmese et al (2013) revealed that 12% of obese people with schizophrenia and schizoaffective disorder met full criteria for NES, demonstrating that NES may contribute to reduced sleep, in turn, leading to hunger and greater propensity to overeat.

Genetic vulnerability also plays a possible role in antipsychotic induced weight gain. This has been supported by the identification of several genes including, α- adrenergic transmission, leptin receptor activity and signalling, promelanin- concentrating hormone signalling, melancorton 4 receptor gene, and cannabinoid receptor activity (Correll et al., 2011; Czerwensky et al., 2013; Malhotra et al., 2012) that have been implicated in weight gain among people with psychosis. However, to counter the effects of antipsychotic induced weight gain, researchers have established beneficial results from metformin administration. In a double- blind study, overweight individuals with schizophrenia or schizoaffective disorder, who were randomly assigned to 16 weeks of metformin, had a -3.0 kg weight loss compared with the placebo group (-1.0 kg weight loss), suggesting that metformin administration is modestly effective in attenuating weight gain (Jarskog et al., 2013).

The etiology of overweight and obesity in people with psychosis is largely influenced by psychosocial factors. In addition, factors relating to social withdrawal and isolation, amotivation (caused by negative symptoms and side effects from antipsychotic therapy), financial hardship, decreased interest in social achievement, single marital status, lower education and unemployment status, create barriers to physical activity engagement and participation (Daumit et al., 2011; Agerbo et al., 2004; Hahn et al., 2014a). These hindrances pose great difficulty in achieving exercise, especially where limited financial resources make it difficult to purchase healthy foods to promote weight loss. Furthermore, substance misuse including alcohol, tobacco and cannabis that is also common in psychosis compared with the general population (Thornton et al., 2013) contributes to an unhealthy lifestyle, limiting access to resources like exercise programs and shops that sell healthy groceries, all of which promote a healthier lifestyle.

A recent systematic review and meta-analysis, using 20 research papers, examining exercise interventions in people with schizophrenia, reported no consistent decline in body weight and BMI post exercise interventions (Firth et al., 2015). However, the authors' report a significant reduction in waist circumference (-4.3cm) following 14 weeks of exercise, suggesting this abdominal obesity may be a more appropriate target compared with BMI, as previously, waist circumference has proved more useful than BMI for measuring cardiometabolic health risks (Janssen et al., 2004). Furthermore, perspectives on behavioural interventions for weight loss, suggest that programs need to target the control of appetite since properties of psychotropic drugs can increase hunger (Werneke et al., 2013). While interventions targeting weight in people with psychosis have shown positive results through the promotion of weight management, physical activity and nutrition advice (Happell et al., 2012), it appears that strategies to cope with hunger would provide further benefits to decrease caloric intake. Long term, tailored interventions promoting physical activity education and a healthy diet is warranted to sustain long term results.

Physical Inactivity

Insufficient physical activity is a major contributing factor for the progressive development of cardiovascular disease. Exercise promotes weight loss and ultimately this can have favourable effects on reducing other metabolic risks that are responsible for CVD and the metabolic syndrome, including: diabetes, hypertension and high cholesterol (Williams and Thompson, 2013). Other benefits of exercise also extend to increasing bone and muscle strength (Yuan et al., 2015), decreasing the risk of cancer (Wu et al., 2013; Anzuini et al., 2011) and improving mental health and quality of life (Vina et al., 2012). However, the question is how much

physical activity is sufficient to reduce the risk of chronic disease and to maintain good overall health?

National physical activity guidelines recommend that adults should engage in 150-300 minutes of moderate or 75-150 minutes of vigorous activity, or an equivalent combination of both, per week (Australian Bureau of Statistics, 2015). Almost thirty percent (29.7%) of men and women in the national population fail to meet these recommendations, while 14.8% are inactive or sedentary (Australian Bureau of Statistics, 2015). A higher proportion of men compared with women (57.7% versus 53.3%) aged 18-64 years appeared to meet guidelines. However, WHO recommendations are slightly less restrictive proposing that 150 minutes per week of moderate-intensity activity or 60 minutes per week of vigorous activity is a sufficient target for beneficial health outcomes in the general population (WHO, 2009). While the benefits of physical activity on cardiovascular health have received considerable attention in the general population (Naci and Ioannidis, 2015), research regarding the importance of physical activity in people with schizophrenia only began to emerge within the past two decades. There is research demonstrating that people with schizophrenia are falling well below physical activity recommendations. Findings by Vancampfort et al (2013), reported that people with schizophrenia (n = 80) were three times less likely to engage in moderate activity and two and a half times less likely to participate in vigorous activity compared with healthy controls (n = 40) and 41.2% were physically inactive (Vancampfort et al., 2013). A study comparing physical health parameters in people with psychosis and the general population revealed that people in the latter group were more likely to engage in all domains of physical activity, including: total leisure, total work, moderate activity, vigorous activity and overall total physical activity (Northey and Barnett, 2011). The lack of physical activity in people with psychosis compared with their non-psychosis counterparts has been consistent across many studies (Roick et al., 2007; Sorensen, 2006).

The disparity in physical activity between people with psychosis and the general population may be related to the unique challenges that people with schizophrenia face in adopting an active lifestyle. Common factors affecting participation in physical activity have previously been related to: medication side-effects, positive and negative symptoms from having a psychotic illness, lack of social support, decreased self-esteem, unemployment and lack of community access promoting opportunities to exercise (Roick et al., 2007; Ussher et al., 2007; Schmitz et al., 2004), all of which decrease a person's motivation to participate in physical exercise. An important factor further compounding physical activity may be related to the persistent use of substances (tobacco, cannabis and alcohol) (Moore et al., 2012; Hahn et al., 2014a) whereby the negative health outcomes and drug effects associated with their use

(breathing difficulty and alterations of consciousness) may decrease participation in exercise. Importantly, a large proportion of the psychosis population are obese (47.4%) (Morgan et al., 2014). Vancampfort et al (2012) reported that people with schizophrenia who exceeded a sitting time of more than 10.4 hours a day, had a higher BMI, waist circumference, and fasting glucose concentrations, and experienced more negative and cognitive symptoms in contrast to those sitting less than 5.8 hours per day (Vancampfort et al., 2012b). More recent evidence from a systematic review and meta-analysis showed that people with psychosis spend an average of 11-12 hours being sedentary (Stubbs et al., 2016).

Due to the complex profile of people with psychosis, it has been recently argued that adhering to physical activity guidelines that are recommended to people in the general population, poses significant challenges to individuals with psychosis; thus, these guidelines should instead, be set as 'aspirational goals' (Stubbs et al., 2014). A number of systematic reviews and meta-analyses have shown that the inclusion of some physical activity as part of intervention programs produces multiple health benefits and therefore, should form an essential part of the multidisciplinary treatment of schizophrenia (Vancampfort et al., 2010; Vancampfort et al., 2012a; Vancampfort et al., 2014; Rosenbaum et al., 2014; Firth et al., 2015). Recent evidence summarising data from randomised controlled trials (RCT's) relating to the efficacy of physical therapy interventions in the management of schizophrenia (n =549) within a multidisciplinary care approach, revealed that aerobic exercise and yoga significantly reduced psychiatric symptoms, improved mental health and physical quality of life, and reduced metabolic risk and weight (Vera-Garcia et al., 2015). While this does indicate that exercise is feasible in the psychosis population to produce beneficial health outcomes, intervention trials predominantly consist of modest duration and the type of physical activity that is administered is not usually tailored around the individual's needs. Several authors have stated that the focus of interventions targeting physical activity should not be related to efficacy, but instead, focussed on how individuals with schizophrenia can include physical activity within their daily lives in a realistic and practical manner (Vancampfort et al., 2015b; Vancampfort et al., 2015a). Authors have suggested that by adopting small and incremental changes within the individuals environment (i.e., getting up from the chair and moving around during television commercials or adding 5-minute walks throughout the day) can help reduce sedentary behaviour and help transition individuals into exercise (Vancampfort et al., 2015a). It is thought that by conducting incremental exercises in a home-based setting, individuals will not be constrained by environmental, socio-economic or organisational barriers (Vancampfort et al., 2015a) that ultimately make participation in exercise difficult to achieve. Furthermore, current findings are predominantly based on cross-sectional studies,

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highlighting the need for longitudinal and interventional designs, incorporating long term follow-up, in order to better understand the relationships between physical inactivity and psychosis. Using qualitative methods over quantitative research methods, may provide a better understanding of individuals' perceptions regarding physical activity and may indicate how such services can be specifically tailored around individual's needs (Soundy et al., 2014).

Low fruit and vegetable intake

Inadequate consumption of fruit and vegetables is estimated to cause 11% of deaths from ischemic heart disease and 9% of deaths from stroke (WHO, 2009). There is evidence that sufficient consumption of fruit and vegetables may reduce the risk of chronic diseases, such as coronary heart disease (CHD) stroke, Type 2 diabetes and obesity (Boeing et al., 2012) by providing healthy nutrients including vitamins, potassium, folate, fiber and other phenolic compounds. These nutrients have a number of beneficial effects in the body such as increasing insulin sensitivity, improving homeostasis regulation, reducing antioxidant stress and free radicals and improving lipoprotein profile, which can reduce the risk of disease and maximise good health (Slavin and Lloyd, 2012).

In the general population in Canada (n=15,512), approximately 77% of adults aged 18-64 years consume less than 5 daily servings of fruit and vegetables (Dehghan et al., 2011). That is, more than three quarters of adults in the normal community fail to meet WHO dietary recommendations. Research relating to fruit and vegetable consumption in people with psychosis is lacking, particularly in consideration of the WHO dietary criteria. However, there is some evidence that people with psychosis have a lower intake of fruit and vegetables compared with the normal population, relative to their daily mean intake of these food groups. A study by McCreadie et al (2003) examining risk behaviours for CVD in schizophrenia, highlighted an average consumption of 16 portions of fruit and vegetables per week, approximately equivalent to 2.4 servings of fruit and vegetables per day, which falls below the average consumption in Australia and Europe (3-4 servings of fruit and vegetables per day) (Leenders et al., 2013; Daly et al., 2011). Similarly, Fusar-Poli et al (2009) highlighted an average daily consumption of 2.2 servings of fruit and vegetables among people with functional psychoses. There is also limited data comparing nutrient intake among individuals with psychosis and the general population. One study by McCreadie and colleagues (2003) revealed that HDL-cholesterol, vitamin C and β-Carotene, were outside normal ranges in 42-53% of people with schizophrenia, but no statistical comparison of nutrient intake was made with the normal population. In addition to this, further research has suggested that people with schizophrenia have an even worse diet than the general population due to their increased

consumption of saturated fat (Ryan et al., 2003), sucrose and sweetened drinks (Elmslie et al., 2001) salt (Davidson et al., 2001) fast food, salty snacks and sweets (Kilian et al., 2006).

Of the very few studies that have examined the dietary profile among people with psychosis, sample sizes have been relatively small (n = 62-219), limiting the generalisability of findings (McCreadie and Scottish Schizophrenia Lifestyle, 2003; Simonelli-Munoz et al., 2012; Roick et al., 2007; Fusar-Poli et al., 2009). However, findings by Roick et al (2007) revealed that male gender, lower educational attainment and unemployment predicted the consumption of unhealthy groceries (Roick et al., 2007). In light of this, research exploring the risks associated with a poor diet is still lacking. A larger study by Kilian and colleagues (2006) (n = 363) demonstrated that unhealthy nutrition habits (consuming ready-to-serve meals several times per week, never eating fresh fruit or vegetables, eating salty snacks and sweets every day and eating fast food several times per week), decreased with increasing age and decreased with higher levels of education; being male and married also predicted unhealthy nutrition habits (Kilian et al., 2006). However, while this study included people diagnosed with a psychotic illness (schizophrenia and bipolar disorders), it also included people without a psychotic diagnosis (major depressive disorder, neurotic and somatoform disorders), thus, the findings are not generalisable to people with psychotic illness. More research is needed to better understand the relationship between poor dietary behaviour and psychosis.

It is likely that the unhealthy diets in people with psychosis may be compounded by low physical activity levels and sedentary behaviour, which are highly prevalent in this population (Vancampfort et al., 2016; Stubbs et al., 2016). Over the past 15 years, clinical studies and animal studies have demonstrated that increased appetite, increased food intake and delayed satiety signalling are key behavioural changes associated antipsychotic induced weight gain and obesity (Deng et al., 2010; Blouin et al., 2008; Sentissi et al., 2009). Individuals treated with second generation antipsychotics (clozapine, olanzapine, risperidone or quetiapine have previously exhibited greater adiposity and increased hunger following a standardised breakfast compared with controls and were more reactive to external eating cues compared with the control group (Sentissi et al., 2009). In a randomized double blind study, individuals receiving olanzapine were more likely to have higher rates of food cravings compared with people taking clozapine (23.3% versus 48.9%) and were more likely to binge eat (16.7% versus 8.9%) over the 6-week treatment period (Kluge et al., 2007). Socioeconomic disadvantage, that is highly common in people with psychosis, often reflected by unemployment and low financial income (Sweeney et al., 2015), further exacerbates diet

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quality as fast food and lower quality foods are chosen for consumption over healthier foods due to affordability and convenience.

The link between poor diet and poverty is evident in people with psychosis as well as people in the general population (Leung et al., 2012). However, earlier studies have suggested that individuals with schizophrenia have an even worse diet compared with the lowest socioeconomic class of the normal population (McCreadie and Scottish Schizophrenia Lifestyle, 2003; Brown et al., 2000). While similar barriers to healthy eating have been found in people with psychosis and the general community (low financial income, limited access to healthy food choices, lack of mutual engagement and unhealthy social environments) (Aschbrenner et al., 2013), people with psychosis face further, unique challenges such as increased appetite and adverse metabolic effects from antipsychotic medications, lack of communications skills, limited social support (Sweeney et al., 2015; Young et al., 2015) and positive and negative symptoms that further exacerbate poor dietary patterns. Interventions targeting diet in psychosis have been successful by actively demonstrating ways to eat healthier. For example, conducting shopping trips to local grocery stores to reveal healthy options among available choices, and taking participants to nearby restaurants or fast food establishments to highlight healthier food options have resulted in a significant reduction in weight and the metabolic syndrome (Cabassa et al., 2010; Bradshaw et al., 2005). However, a randomised control study held over 6 months (7 individual face-to-face sessions) using a healthy living intervention characterised by: psychoeducation, participatory exercises and dietary change through the development of patient-centred goals and action plans, revealed no significant reduction in weight in psychosis participants compared with participants in the treatment as usual (TAU) group (some level of support but no systematic approach to weight control) (Lovell et al., 2014). This suggests that people with psychosis may respond better to practical dietary support performed in natural environments as demonstrated by Cabassa et al (2010) and Bradshaw et al (2005) as opposed to more structured interventions. It may possibly also be the case that people with psychosis require more face-to-face contact and ongoing support to produce favourable outcomes.

High blood pressure

High blood pressure has been identified by WHO as a leading risk factor for mortality around the world (WHO, 2009). The WHO reports that 51% of stroke deaths and 45% of ischemic heart disease deaths are attributed to high systolic blood pressure (WHO, 2009). Raised blood pressure changes the structure of the arteries, causing damage to arterial walls through microscopic tears that develop into scar tissue. Consequently, circulating materials including

cholesterol, platalets and fat (known as plaque) become trapped in the scar tissue causing the arteries to narrow and harden; ultimately, this can increase the risk of stroke, heart disease, kidney failure and other chronic diseases (American Heart Association, 2014).

The prevalence of hypertension defined by systolic/diastolic blood ≥140/90 mmHg is different in the normal population and in people with psychosis relative to if a person is treated with antihypertensive medication. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study ($n = 1460$), showed that among people with hypertension, 37.6% of participants were receiving treatment for this condition and 62.4% of participants were not receiving treatment. (Nasrallah et al., 2006). This is considerably higher compared to the prevalence of treated (19.0%) and untreated hypertension (13.1%) in the normal population ($n = 2425$) (Appleton et al., 2013). This disparity between rates of untreated and treated hypertension may reflect inequality of health care among primary medical services and barriers faced by people with psychosis in accessing public health clinics. Including people with both treated and untreated hypertension, the prevalence of hypertension in people with schizophrenia and people in the normal population is relatively comparable (33.2% versus 32.1%) respectively (Nasrallah et al., 2006; Appleton et al., 2013). The lack of age standardisation across both populations may account for this comparable hypertension estimate. Research by Galletly et al (2012) has also reported a high prevalence of hypertension among individuals with psychosis; 42.1% of individuals with untreated hypertension and 6.5% with treated hypertension (Galletly et al., 2012).

Research has also investigated systolic blood pressure (SBP) and diastolic blood pressure (DBP) in psychosis. These measure different components of blood pressure. Systolic blood pressure measures the amount of pressure in the arteries when the heart contracts and DBP measures the amount of pressure in the arteries when the heart rests between beats. It has been shown that at age 25, DBP was significantly higher in people with psychosis compared with controls (Foley et al., 2013); other work revealed a higher incidence of systolic hypertension in men compared to women with psychosis and in people aged 35-64 years compared with individuals aged 18-34 years with psychosis (Galletly et al., 2012). There has also been work done regarding blood pressure in people with psychosis relative to other metabolic risks. For example, hypertension is much higher in people with schizophrenia who have a diagnosis of diabetes (64%) compared to people with schizophrenia who are not diagnosed with diabetes (29%) (Dixon et al., 2000). Being overweight or obese which is common to schizophrenia, also increases the risk of hypertension and diabetes (Depp et al., 2014). More recent evidence among people with psychosis showed that SBP was positively correlated with BMI, diastolic blood pressure, and waist circumference while DBP was

positively correlated with BMI, waist circumference, total cholesterol, triglycerides and systolic blood pressure; all the correlations with SBP and DBP were significant (Foley et al., 2013).

For many decades, authors have highlighted the utility of SBP and DBP in predicting risk of CVD. Historically, DBP was regarded as a better predictor than SBP because it was believed to represent the resistance that the heart had to overcome to eject blood (Macwilliam and Melvin, 1914). However, in the 1970's and 1980's SBP was considered as a more useful predictor of coronary heart disease, stroke and heart failure; and was shown to be superior to DBP in predicting CV risk among older people (beyond 50 years of age) (Kannel et al., 1971; Stamler et al., 1989; Rutan et al., 1989). This is because, in western society, (SBP) begins to rise steadily with age due to increased stiffness of the large arteries; diastolic blood pressure (DBP) increases in parallel with SBP up until age 50, then trends downwards while SBP continues to increase (Lewington et al., 2002). More recently, attention has been shifted towards the relative importance of other blood pressure components in predicting CVD risk outcomes. Pulse pressure (PP) and mean arterial pressure (MAP), which are derived from SBP and DBP (PP= SBP-DBP); (MAP= [(2 x diastolic) + systolic]/3) have also been considered to be associated with CVD risk. Pulse pressure reflects stiffness of the large arteries which increases with advancing age due to the opposing trends in SBP and DBP (De Henauw et al., 1998; Staessen et al., 2000) and MAP is a measure of cardiac output and peripheral resistance (Franklin et al., 2009; McGhee and Bridges, 2002). Based on results from the Framingham Heart Study, Franklin et al (2009) demonstrated that combining SBP with DBP and PP with MAP, were superior to single BP components in predicting CVD risk; combined SBP + DBP and combined PP+MAP were equally predictive of CVD risk (Franklin et al., 2009). This has been supported by Domanski et al (2002).

Pulse pressure and mean arterial pressure can help to understand the relative function of both stiffness and resistance in contributing to CVD risk, thus, providing additional information to systolic and diastolic blood pressure. In contrast to these findings, earlier studies by Franklin et al (1999) and Benetos et al (1997-99) suggested that PP is a better predictor of increased risk of coronary heart disease than SBP or DBP; and PP is a significant an independent predictor of myocardial infarction (Franklin et al., 1999; Benetos et al., 1998; Benetos et al., 1997; Benetos, 1999). Taken together, these findings demonstrate that PP and MAP are clinically useful and deserve further attention.

While there is some disagreement about what constitutes a true risk level for PP and MAP, some studies in the normal population, suggest that a PP of 63 mmHg or greater, and a

MAP value of 97 mmHg or greater, can more than double the risk of developing CVD (de Simone et al., 2005; Weiss et al., 2009; Sesso et al., 2000). However, these thresholds have not been well-validated. There has been considerable research into these blood pressure components among people without a psychotic illness (Kodama et al., 2014; Rapsomaniki et al., 2014; Livingstone et al., 2013; Safar et al., 2015; Pase et al., 2015). However, few studies have explored pulse pressure in psychosis. One study revealed a slightly higher PP in first episode psychosis patients (42.7 mmHg) compared to matched controls (41.7 mmHg) adjusted for age, gender and ethnicity, but this did not reach statistical significance (Sengupta et al., 2008). Another study found significant findings for pulse pressure in anti-psychotic naïve patients with schizophrenia and matched controls (47.9 mmHg versus 41.8 mmHg) (Fernandez-Egea et al., 2009b). A pilot study by Phillips et al (2014) revealed a higher MAP in schizophrenia individuals (89 mmHg) compared with matched controls (83 mmHg) but this was not statistically significant. However, more work is needed to understand arterial stiffness (PP) and peripheral resistance (MAP) in older people with psychosis. It would be hypothesised that PP and MAP would increase with age and duration of antipsychotic treatment.

Despite the utility of PP and MAP in providing a broader image of CVD risk in relation to arterial elasticity and peripheral perfusion, there have been few studies investigating these blood pressure components relative to age, gender and other risk factors that are known to affect blood pressure. One large study (n = 2813) explored sociodemographic, clinical and lifestyle characteristics in relation to PP and MAP (Tyrovolas et al., 2014); another study (n = 5771) explored PP in relation to age, metabolic indices and smoking (Domanski et al., 2001) however; these studies were performed among people in the general population. The associations of PP and MAP in people with psychosis remain unknown. A recent study in Taiwan investigated the effects of high intensity interval training (HIIT) on blood pressure subtypes including PP and MAP among individuals with chronic schizophrenia (Wu et al., 2015). The intervention was characterised by a 5-minute period of warm up, followed by 15 period of HIIT (full-effort exercise boosting heart rate to 85%–95%), then 5-minute period of stretching, 3 days a week for 8 weeks. There was a significant reduction in mean PP (-10.78) from baseline to post-intervention however, MAP increased from baseline to post-intervention (+3.25) (Wu et al., 2015). The reduction in mean PP in the former study is encouraging. It has been previously shown that increases in PP can adversely affect arterial walls, leading to atherosclerosis and thrombosis (Domanski et al., 2002; Domanski et al., 2001). It should be noted the former study consisted of a small sample size and warrants replication among a larger sample of participants. Better CV outcomes

associated with HIIT, compared with moderate intensity interval training has been established in the general population and in individuals with schizophrenia (Herbsleb et al., 2014; Chalfoun et al., 2015) but these studies did not measure PP or MAP.

CONCLUSIONS

Taken together, the above WHO-defined risk factors are more prevalent in people with psychosis, compared with the general population, adding support to their detrimental health profile and excess mortality. This literature review has shown that psychosis is associated with unique risks (genetic predispositions, antipsychotic medication side effects, adverse social environment, and poor access to health care and poor quality of health care) in addition to the above traditional risks that further exacerbate physical health and increase the onset of cardiovascular illness. The interplay between these factors and psycho-social factors, including stigma, social isolation, lack of social support and low-socio-economic status, creates significant barriers in addressing poor health behaviours. Therefore, this suggests that the underlying reasons for the development of cardiovascular disease in this population are multi-factorial and complex. In order to modify these risks and improve cardiovascular health and wellbeing in people with psychosis, health workers must understand how these risks are connected to each other and recognise the broader picture of how these risks emerge. The depiction of the physical health status among people with psychosis in this thesis is highly warranted to narrow the gap in health care access and utilisation, and in health care provision. The growing problem of medical comorbidities and premature death among this population needs an urgent call to action and this thesis attempts to clarify the kinds of factors that may be responsible for such physical health conditions. Ultimately, this may inform treatment guidelines and recommendations at the system level (state and health care institutions) and individual level (clinicians, patients and family) in the hope of also increasing government funding so mental health workers can deliver the appropriate interventions and level of health care that is necessary to improve the overall quality of life among people with severe mental illness.

Chapter 2: Exegesis

Justification and overview of research project

The World Health Organisation (WHO) plays a vital role in the global governance of health and disease. It aims to improve health equality, reduce health risks, promote healthy lifestyles and respond to the underlying determinants of health. It is apparent that eight health risk factors: alcohol use, tobacco use, high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake and physical inactivity, account for 61% of loss of healthy life years from cardiovascular diseases and 61% of cardiovascular (CV) deaths around the world. However, there has been no full investigation into these eight risk factors among people with psychotic illness, despite research identifying that this population are at a greater risk of cardiovascular disease (CVD) and excess mortality compared with the normal population.

Over the past decade, there has been almost an exponential increase in research regarding CV outcomes in psychosis, measured by the relative risk (RR) of a CV event occurring based on the risk factor profile of the psychosis population. While this has indeed broadened our understanding of the underlying risk factors that may in-part explain premature mortality in people with psychosis and alert health care workers to appropriate interventions, there still remains a gap in the research literature relating to the evaluation of individual CV risk factors in terms of their associations with other risk factor variables, and the quantification of overall CV risk factors in people with psychosis. Exploring these issues is paramount for a number of reasons. Firstly, the identification of CV risk associations can ultimately inform health care workers at the clinical and intervention level to enable them to target known risks and prevent CV illness. Secondly, a summation of the 8 WHO-defined risk factors in people with psychosis can be clinically useful in providing an absolute number of CV risks to help identify high- risk patients who need immediate attention and intervention; and possibly, to serve as a tool for motivating patients to adhere to risk-reduction therapies. The health risk factors outlined by WHO are crucial targets in people with psychosis since they are the primary risks responsible for cardiovascular-related mortality, which is the leading cause of death among this population.

Before presenting my research papers, it is important to understand the research study that was undertaken, and how my research fits in context with other research that was conducted among the same study participants.

The majority of my research was based on the 2010 Australian National Survey of High Impact Psychosis, which I will refer to as the 'SHIP' study (Morgan et al., 2011) . This study comprised of 1825 individuals diagnosed with a psychotic illness, assessed at seven catchment sites across Australia. A number of domains were assessed in the SHIP survey including demographics, social participation and functioning; quality of life; psychopathology; cognitive profile; substance use; service use and perceived needs. In addition, part of my research was also based on a subset of participants from the SHIP study that were surveyed in South Australia. This study comprised of 184 participants who provided additional information relating to diet, sleep and ECG assessments. Participants from the South Australian catchment site were less likely to be employed or complete high school compared with participants across the remaining catchment sites in Australia. Participants were selected from the northern suburbs in South Australia, which is known to have higher rates of socio-economic disadvantage compared to the other catchment sites from where the other participants were surveyed.

During my research candidature, my aim was to focus on the physical health component of this study covering areas relating to nutrition, physical activity, physical health and metabolic measures. My role was to also focus on the detailed dietary information that was obtained from a smaller number of participants in South Australia. Out of the 8 WHO-defined risk factors, research relating to diet, blood pressure and the total number of CV risk factors present had not been undertaken among the SHIP cohort. An examination of alcohol consumption (Moore et al., 2012), tobacco use (Hahn et al., 2014a; Cooper et al., 2012), diabetes (Foley et al., 2014; Foley et al., 2015b; Foley et al., 2015a; Foley et al., 2013), cholesterol and overweight or obesity (Foley et al., 2013; Galletly et al., 2012) among this sample of people, had been previously published, thus, it was important to focus on the remaining risk factors that had not yet been thoroughly explored. This chapter reviews each of my five manuscripts, and will include a discussion on why my research was warranted, based on previous research findings in the literature, and research findings that have been published by the SHIP research team.

Section A: Individual Risk Factors for Cardiovascular Disease (CVD)

Paper 1

The purpose of the first paper was to assess factors that may be related to low fruit and vegetable intake in a national sample of people with psychosis. Indeed, the few studies that have been published in this area have shown that the diets of people with psychosis is rather

poor; however, these studies have been limited by small sample sizes (n = 62-219) and were conducted in European countries. Therefore, I felt that these studies needed to be replicated using a larger sample of people with psychosis, in order to broadly explore potential dietary associations, as in past studies, diet has not been the sole focus of the authors' papers (Roick et al., 2007; Fusar-Poli et al., 2009; John et al., 2009). Furthermore, while we know that poor diet is part of a constellation of health risk factors commonly known to psychosis, we do not know what characteristics are common to those who have an inadequate diet. Thus, it remained untested whether a poor diet, represented by a low intake of fruit and vegetables, was accompanied by other unhealthy behaviours. According to WHO, low fruit and vegetable intake is estimated to cause around 11% of deaths from ischemic heart disease and 9% of deaths attributable to stroke (World Health Organisation, 2009). Therefore, it made sense to examine diet in people with psychosis and unpack underlying factors that may influence this poor eating behaviour, which ultimately contributes to the development of CVD. This paper makes an important contribution to the research literature because to date, no other study has examined dietary consumption in psychosis, in the context of whether it adheres to WHO dietary recommendations. It was intended that, by doing this, we would obtain a national estimate of the prevalence of people who fail to conform to these guidelines that could be very useful at the clinical level.

Paper 1 aimed to extend findings by Fusar-Poli et al (2009). Their study did not reveal significant associations between mean fruit and vegetable intake, and regular exercise or metabolic risk factors (Fusar-Poli et al., 2009). It was therefore, necessary to repeat this study using a larger sample of people to determine if, in fact, any of these factors are related to diet. Also, due to the lack of association between diet, exercise and metabolic risks in Fusar-Poli et al (2009) study, it was important to assess additional risk factors in my paper (demographics, substance use, and diagnoses) to ascertain whether they may be associated with inadequate fruit and vegetable consumption. By doing this, it was anticipated that paper 1 could provide an overall picture of what dietary behaviour looks like among people with psychosis and the factors that may be influencing fruit and vegetable consumption. This would also extend work by Roick et al (2007) where dietary intake was investigated in individuals with a schizophrenia diagnosis. My research paper, however, explores dietary behaviour in people diagnosed with schizophrenia and also people diagnosed with other psychotic disorders.

Paper 2

Paper 1 provided quantitative evidence that inadequate consumption of fruit and vegetables was linked to an array of other poor health behaviours and demographic factors. Thus, the aim

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of paper 2 was to extend these findings by unpacking fruit and vegetable consumption with a focus on macro and micro-nutrient intake in a smaller sample of people with psychosis residing in the northern suburbs of Adelaide. Unlike paper 1, where diet inadequacy was defined in accordance with WHO guidelines, paper 2 attempted to measure nutrient deficiency by referring to Australian guidelines on the recommended dietary intake (RDIs). Based on a smaller study in Scotland, we know that people with schizophrenia fall below the target range on some nutritional measures (McCreadie and Scottish Schizophrenia Lifestyle, 2003). However, I planned to extend these findings, by selecting a number of nutrient variables that have been widely investigated in the general population and associated with CVD risk. I was further interested in determining whether nutrient composition in psychosis differed to that of the general population in terms of meeting the RDI's. No other study has explored nutrient RDI's in psychosis and importantly, little research exist comparing nutrient RDI's with the normal population. Thus, paper 2 was warranted to further investigate dietary composition at the micronutrient level, and to provide a broader summary of participants' dietary intake relative to the normal population.

Paper 3

Paper 3 is an important paper that extends prior research among this cohort of people with psychosis. This previous research on the SHIP project had revealed striking findings relating to cardiometabolic risk associations, and the trajectory of these risks by age and gender, compared with the normal population. Importantly, it was discovered that approximately 20% of individuals had hypertension (over 50% for those who fasted for blood tests); more than three quarters had diastolic hypertension and almost one third had systolic hypertension (Galletly et al., 2012). In addition to this, diastolic blood pressure (DBP) and systolic blood pressure (SBP) was positively correlated with a number of biomedical risk factors, including: age, BMI, waist circumference, total cholesterol, LDL cholesterol and triglycerides (Foley et al., 2015c). Further research among the SHIP cohort revealed that from age 25, individuals were already presenting with a higher mean SBP and DBP compared with the general population aged 25 years and onwards (Foley et al., 2013). Based on this evidence, I decided to continue this ongoing investigation into blood pressure, in part, motivated by the fact that hypertension is the second leading cause of death around the world (World Health Organisation, 2009). Evidence suggesting that hypertension is more common in people with psychosis compared with the general community is alarming and warrants further attention.

Thus, the aim of paper 3 was to examine pulse pressure (PP) and mean arterial (MAP) which are derived from mean SBP and DBP. For almost 20 years, research exploring these

blood pressure indices in people without chronic mental illness, have highlighted the predictive power of PP and MAP in predicting CVD risk (Franklin et al., 1999; Benetos et al., 1998). Research concerning PP and MAP among people with psychosis is scarce; of the few studies that incorporated these components into their blood pressure analysis, only mean PP and MAP were obtained for the study participants. I felt that it was necessary to make a contribution to the very few studies that exist in this research area, regarding these different blood pressure components. Due to this lack of research in this field among people diagnosed with a psychotic illness, it was required that I conduct a literature review in the general population to assess whether any prior studies have in fact, identified any associations with PP and MAP. It was anticipated, that this would provide a framework that could guide my research paper on PP and MAP in people with psychosis and possibly determine whether associations of PP and MAP in the general population would be the same among individuals with chronic mental illness.

In summary, the three papers presented in this section were designed to provide a more thorough understanding of individual CV risks and their relationships with other risk factor variables. The following section of the thesis is intended to provide a broader overview of the 8 WHO-defined risk factors.

Section B: Total Number of Risk Factors Present

Paper 4

It is well known that CV risks in people with psychosis are common and papers' 1, 2 and 3 in this thesis, provides further support for this. However, much less is known about the absolute number of risk factors that are present in each individual. Therefore, the purpose of paper 4 was to draw all of the 8 WHO-defined risk factors together to determine the quantity of risk factors that really exist among this population. This method of 'risk factor counting' has not been done before in people with psychosis, thus, I thought this could be a novel approach in understanding the overall picture of death and disability in this population; after all, these are the major CV risks responsible for morbidity and mortality around the world. Research has demonstrated that CV risks appear at an early stage in the course of psychiatric illness and in young cohorts with psychosis compared with young controls (Mitchell et al., 2013a; Fernandez-Egea et al., 2009a). Foley et al (2013) also established that from age 25, participants from the SHIP study, scored significantly higher on a range of cardiometabolic risks (BMI, waist circumference, triglycerides, diastolic blood pressure) and lower on HDL cholesterol, compared with the normal population. In light of these findings, I saw an

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important opportunity to contribute to the area of early intervention in psychiatry by focussing on multiple CV risk factors in young people with psychosis aged 18-24 years. This seemed like a plausible method for detecting and assessing CV risk at the clinical level in an attempt to target these risks that could ultimately prevent the progression of this illness in younger people. I believe quantifying CV risks is an exciting, new line of research that could help inform and advance future studies on CV risk in young people with first episode psychosis (FEP) and in young people diagnosed with a psychotic illness.

Paper 5

The final paper of this thesis was to continue exploring the count of CV risk factors in people with psychosis aged 18-64 years. Given that people with chronic schizophrenia have a higher prevalence of risk factors for the metabolic syndrome (increased waist circumference, hypertension, increased triglycerides, impaired fasting glucose or diabetes and decreased HDL-C) in comparison to first episode psychosis (FEP) or unmedicated patients, as shown by Mitchell et al (2013), I wanted to test whether age had an effect on the distribution of CV risk factors. Furthermore, I attempted to probe further into the possible effect of gender on the distribution of these risks because, as it stands, men with psychosis generally have a higher prevalence of CV risks than women (apart from obesity). It was therefore, necessary to clarify this, in terms of identifying the total number of CV risk factors present according to men and women. As mentioned in the previous paper, risk factor counting, particularly using the WHO-defined risks has not been done before in people with severe mental illness. Therefore, this work is refreshing as it represents a different and important framework for evaluating CV risks, taking into consideration all of the risk factors that contribute to morbidity and mortality.

Taken together, the two papers presented in this section were formulated to provide a wider overview of CV risks in people with psychosis in terms of multiple risk factors, with a particular focus on age and gender.

SECTION A

Individual Risk Factors for Cardiovascular Disease

CHAPTER 3: Paper 1

Statement of Authorship

Title of Paper	Inadequate fruit and vegetable intake in people with psychosis.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Hahn, L. A., Galletly, C. A., Foley, D. L., Mackinnon, A., Watts, G. F., Castle, D. J., Waterreus, A. & Morgan, V. A. (2014). Inadequate fruit and vegetable intake in people with psychosis. *Aust N Z J Psychiatry,* 48, 1025-35.

Principal Author

Name of Principal Author (Candidate)	Lisa Hahn
Contribution to the Paper	Undertook literature review, performed data analysis, interpreted data, drafted and prepared manuscript, submitted manuscript, responded to reviewers and undertook revisions of the paper.
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 08.03.2016

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Cherrie Galletly
Contribution to the Paper	Commented and edited drafts of manuscripts, made suggestions on the presentation of material in the paper and suggested journal for manuscript submission.
Signature	Date 08.03.2016

Name of Co-Author	Debra Foley
Contribution to the Paper	Edited drafts of the manuscript and made suggestions regarding data analysis and interpretation and the citation of relevant literature.
Signature	Date 09.05.2016

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Name of Co-Author	Andrew Mackinnon		
Contribution to the Paper	Commented and edited drafts of manuscripts and made suggestions on the presentation of material in the paper.		
Signature		Date	10.13.2016

Name of Co-Author	Gerald Watts		
Contribution to the Paper	Commented on drafts of manuscripts and made suggestions on the presentation of material in the paper.		
Signature		Date	07.03.2016

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Signature		Date	08.03.2016

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Signature		Date	09.03.2016

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Contribution to the Paper	Commented and edited drafts of manuscripts and made suggestions on the presentation of material in the paper.		
Signature		Date	04.05.2016

CHAPTER 4: Paper 2

Statement of Authorship

Title of Paper	Psychosis and cardiovascular disease: Is diet the missing link?
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Nenke, M. A., Hahn, L. A., Thompson, C. H., Liu, D. & Galletly, C. A. 2015. Psychosis and cardiovascular disease: is diet the missing link? *Schizophr Res, 161*, 465-70.

Principal Author

Name of Principal Author (Candidate)	Marni Nenke		
Contribution to the Paper	Undertook the literature review, conducted data analysis, interpreted data and drafted manuscript.		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	18.03.2016

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

    i.   the candidate's stated contribution to the publication is accurate (as detailed above);

    ii.   permission is granted for the candidate in include the publication in the thesis; and

    iii.   the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Lisa Hahn		
Contribution to the Paper	Updated the literature review, performed additional analyses, drafted and prepared the manuscript, submitted the manuscript to journal, responded to reviewers and undertook revision to the paper.		
Signature		Date	08.03.2016

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Contribution to the Paper	Commented on drafts and made suggestions on the presentation of material in the paper.		
Signature		Date	07.03.2016

Name of Co-Author	Cherrie Galletly		
Contribution to the Paper	Commented on drafts, made suggestions on the presentation of material in the paper and suggested journal for manuscript submission.		
Signature		Date	08.03.2016

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Schizophrenia Research

Psychosis and cardiovascular disease: Is diet the missing link?

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ARTICLE INFO

ABSTRACT

Objective: To explore the diets of people living with psychotic disorders, and to compare their dietary composition to the general population.

Method: 184 people with psychotic disorders in Adelaide, South Australia completed a food frequency questionnaire. Physical information and mental health status were collected. Outcome measures included energy and macronutrient intake; fish, sodium, fruit and vegetable intake; micro-nutrient intake; body mass index; waist circumference; and diagnoses of diabetes and hypertension. The RDI of nutrients was derived from Australian Government publications. Comparison dietary data was obtained from surveys carried out by the Australian Bureau of Statistics.

Results: The majority of participants were overweight or obese (78%) and 77.5% met the criteria for at-risk waist circumference; and 58% of participants consumed salt and saturated fat in excess of the RDI. Most did not achieve the RDI for fruits and vegetables (97.8%), fibre (88.6%), fish (61.4%), magnesium (73.4%) or folate (86.4%).

Women with psychosis had significantly higher intakes of vitamins and minerals compared to women in the general population. Men and women with psychosis consumed more daily total fat, saturated fat and sodium compared to adults in the Australian population, but lower fibre and vitamin E than their male and female counterparts.

Conclusion: People with psychosis, especially women, report poor dietary choices including increased energy and fat intake, heightening their risk for cardiovascular disease. Women with psychosis report higher intake of vitamins and minerals than women in the general population. Whilst dietary intake contributes to obesity in psychosis, other factors including antipsychotic agents, decreased physical activity and smoking add to the cardiovascular risk.

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1. Introduction

People with psychosis have a shorter life expectancy than the general population (Laurson, 2011), with cardiovascular morbidity contributing significantly to their poor health outcomes. The risk factors for CVD in psychosis not only include the traditional risk factors of smoking, hypertension, obesity, diabetes, decreased physical activity and dyslipidaemia, but also disease-specific and treatment-related factors. Despite increased prevalence of traditional risk factors, people with a psychotic illness are less likely to be adequately screened (Osborn et al., 2007) or treated, with up to 88% of adults with schizophrenia not receiving recommended therapy for their physical conditions (Nasrallah et al., 2006). Many antipsychotic medications are associated with obesity, diabetes and dyslipidaemia (De Hert et al., 2012). However, people

with severe mental illness who are drug naïve still have an elevated relative risk of CVD (Osborn et al., 2007); therefore, other factors must also contribute.

Numerous studies have investigated the association between cardiovascular risk and macro- and micronutrient deficiency or excess. The American Heart Association has published guidelines on diet and lifestyle recommendations to prevent cardiovascular disease (Lichtenstein et al., 2006). A diet high in fibre, fruit and vegetables, and low in saturated fat, trans fat and salt, has been promoted for cardiovascular health. Several small studies have assessed the diet quality in people with psychotic disorders (McCreadie, 2003; Strassnig et al., 2003; Henderson et al., 2006). However, there have been variations in the study design, such as using dietary recall in the past 24 h (Strassnig et al., 2003) or using a four-day dietary record (Henderson et al., 2006). This suggests that the evidence is inconsistent concerning whether people with psychosis have a poor diet, which would then contribute to the elevated risk of cardiovascular disease in psychosis.

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Table 1
Physical health characteristics, diagnoses, medication and BMI.

Variable		N (%) or M (SD)
Diagnosis		
	Schizophrenia	55 (29.9%)
	Schizoaffective disorder	60 (32.6%)
	Bipolar disorder	26 (14.1%)
	Major depressive disorder with psychosis	10 (5.4%)
	Other	33 (17.9%)
Medication		
	Typical antipsychotic	39 (21.2%)
	Atypical antipsychotic	105 (72.3%)
	Clozapine	28 (15.2%)
	Mood stabilizer	63 (34.2%)
	Antidepressant	83 (45.1%)
	Anxiolytic/hypnotics/sedatives	41 (22.3%)
	Anti-hypertensive medication	16 (8.7%)
	Lipid regulation medication	19 (10.3%)
	Anti-hyperglycaemia medication	8 (4.3%)
Polypharmacy		
	Single antipsychotic (typical or atypical or clozapine)	115 (62.5%)
	Two or more antipsychotic type	41 (22.3%)
	Any anti-psychotic + mood stabilizer	56 (30.4%)
	Any anti-psychotic + anti-depressant	68 (37.0%)
	Any anti-psychotic + anxiolytic/hypnotic/sedatives	34 (18.5%)
Body mass index (kg/m2)		
	Underweight (<18.5)	1 (0.5%)
	Normal (18.5–24.9)	37 (20.1%)
	Overweight (25–30)	56 (30.4%)
	Obese (30<)	85 (46.2%)
	Missing	5 (2.7%)
Blood pressure (mm Hg)		
	Systolic ≥ 130 mm HG	73 (39.7%)
	Diastolic ≥ 85 mm HG	93 (50.5%)
Diagnosed with diabetes		45 (24.9%)
Met criteria for metabolic syndrome		106 (53%)
Current smoker		132 (71.7%)
Physical activity level		
	Sedentary	35 (19.1%)
	Low	77 (42.1%)
	Moderate	55 (30.1%)
	High	16 (8.7%)

We undertook a cross-sectional study of a population with psychosis in order to clarify their dietary composition. If poor dietary choices contribute to the increased risk of cardiovascular disease, then dietary interventions should be a clinical priority.

2. Methods

2.1. Study population

This study was a subset of the second Australian national survey of psychosis. Methodological details of this survey are described elsewhere (Morgan et al., 2013). The present study took part in the Northern Adelaide site, one of the eight survey sites. There were 402 subjects at this site who originally took part in the survey, and they were offered participation in an additional study which included assessments of diet and sleep, and an ECG. Contact information was provided by the Consumer Base Information System (CBIS) Mental Health. Participants were contacted by phone and/or letter to reissue the invitation to participate and 210 people responded. A total of 184 participants completed the assessment. Participant loss was due to unwillingness to participate in the study or patients being unreachable. The 184 subjects who agreed to this further study, and completed the assessment, did not differ in age, gender or diagnosis from non-participants.

Ethics approval was obtained from the Queen Elizabeth Hospital Ethics Committee.

2.2. Data collection and dietary assessment

Data were collected in a face to face interview. Each participant completed The Cancer Council Dietary Questionnaire (DQES; Ireland et al., 1994), which reports diet over the last 12 months. A trained researcher assisted with clarification of terms when required. The Cancer Council analyses the nutritional content of the DQES using the Nutrient Table for use in Australia (NUTTAB95) database (Lewis et al., 1995).

The Diagnostic Interview for Psychoses (DIP; Castle et al., 2006) was used to make ICD-10 diagnoses. Methods for collecting anthropometric data including blood pressure, height, weight, waist circumference and plasma collection for glucose and lipid analysis have been described (Galletly et al., 2012). Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) and included four categories of physical exercise: sedentary, low, moderate and high (Craig et al., 2003). Participants were asked about smoking status, medications they had taken in the last month, and if they had ever been diagnosed with diabetes (or high blood sugar) or hypertension. Metabolic syndrome was defined using the harmonized criteria developed by the International Diabetes Federation Task Force on Epidemiology and Prevention

and related expert organizations (Alberti et al., 2009). We compared our results with the Australian recommended daily intake of various foods (National Health and Medical Research Council, 2006) and data from the 2011–12 Australian Health Survey conducted by the Australian Bureau of Statistics, (2014) which included people aged 19–71+ years.

2.3. Data analysis

The statistical package used for data analysis was Statistica '99 Inc., Tulsa OK. The test employed was 'Difference Between Two Means' and the p level was computed based on the t-value for the retrospective comparison. A value of $p < 0.05$ was taken to indicate significance and results are reported as mean ± (SD).

3. Results

The mean age of participants was 39.4 years (± 9.6) and 54.9% were male. Eighty-five percent were taking antipsychotic medications (Table 1). Ten participants took no medications and 130 (70.7%) were taking multiple medications. Ninety-nine percent (n = 183) had left school before completing year 12. About a quarter (23.4%, n = 43) had been in paid employment in the past year. Most people received government benefits (n = 175, 90.8%). The majority of participants (66.3%) had an income between $500 and $799 per fortnight. The mean Australian disposable income at the time of this study was $848 per week (Australian Bureau of Statistics, 2011). Physical activity was low in 42.1%, moderate in 30.1% and high in 8.7% of participants.

Hypertension and diabetes were diagnosed in 19.1% and 24.9% of participants respectively. People taking clozapine had higher rates of diabetes (35.7% vs 22.4%, NS). Women had higher rates of obesity (BMI > 30) than men (51% vs 44%, $p = 0.32$), and 79% of women and 76% of men met criteria for abdominal obesity (waist circumference ≥94 cm in males and ≥80 cm in females). Only one-fifth of subjects met primary prevention recommendations for levels of low-density

lipoprotein (LDL) cholesterol (<2.5 mmol/L), with an average LDL-cholesterol level of 3.2 mmol/L (SD ± 1.0).

Dietary analysis revealed that carbohydrates contributed 42% of total energy, fat contributed 37.8%, and protein contributed 20.2% (see Table 2). The majority of participants consumed less carbohydrate and more fat than the recommended dietary intake (RDI). The RDI is 45–65% and 20–35% of total energy intake for carbohydrate and fat respectively. Most participants consumed saturated fats in excess of the RDI (i.e. 10% total energy intake) and fell below the target for fibre consumption (38 g/day for men, 28 g/day for women). Only three participants consumed the recommended two serves of fruit and five serves of vegetables per day.

Intakes of red meat exceeded recommendations, with 59.2% of patients eating more than two serves of red meat per week. Only 18% of participants consumed fish. Fifty-nine percent consumed full fat milk compared with other varieties. On average, micronutrient consumption including iron, niacin, phosphorus, riboflavin, thiamine, Vitamin C, and vitamin E was above RDI. One third reported consuming no alcohol, but 45% consumed more than two standard drinks per drinking session, with 12% consuming 19 drinks or more in a maximum session.

Comparing men and women in the current sample to men and women in the general population revealed significant gender differences. In comparison to women with psychosis, women in the general population had significantly lower daily intake of energy, protein, mono-saturated fat, poly-unsaturated fat, fish, iron, phosphorous, potassium, zinc, niacin equivalents and thiamin. Both men and women in the Australian population had significantly lower daily intake of total fat, saturated fat and sodium and significantly higher consumption of fibre and vitamin E compared to men and women in the current study.

There was a significantly higher intake of magnesium among men in the general population versus men with psychosis. Alcohol intake was higher among the Australian population (both men and women) compared to adults with psychosis, although this was not

Table 2
Nutrient intakes comparing the current study population and the National Nutritional Survey (NNS).

Nutrient	Current study population mean (SD)		Current study population		NNS[*] mean (SD)			
	Male n = 101	Female n = 83	Above RDI (%)	Below RDI (%)	Male n = 4231	p value[**]	Female n = 5007	p value[**]
Energy (kJ/day)	9507.0 (4150.3)	8959.0 (5590.1)	NR	NR	9954.5	0.39	7420.3	0.0 01
Carbohydrate (g/day)	237.0 (105.8)	216.9 (115.4)	0.5	63.6	258.8	0.19	193.8	0.09
Sugar (g/day)	106.9 (58.0)	105.4 (61.3)	NR	NR	115.2	0.46	90.9	0.06
Protein (g/day)	110.4 (51.2)	112.7 (114.3)	7.1	6.5	104.6	0.39	77.9	0.000
Total fat (g/day)	99.6 (48.2)	92.7 (68.3)	77.7	0.5	83.7	0.008	64.2	0.000
Sat fat (g/day)	41.7 (21.2)	39.1 (28.4)	94.6	NLL	31.5	0.000	24.0	0.000
Mono fat (g/day)	35.6 (17.4)	33.3 (27.1)	NUL	NLL	32.3	0.19	24.5	0.000
Poly fat (g/day)	14.0 (7.7)	12.4 (8.8)	1.1	46.2	12.7	0.28	10.2	0.03
Fibre (g/day)	20.4 (9.7)	19.8 (10.8)	11.4	88.6	24.8	0.02	21.1	0.54
Sodium (mg/day)	3272.9 (1520.5)	3036.0 (2483.3)	59.2	NLL	2779.2	0.007	2090.4	0.000
Fruit & veg (g/day)	257.7 (203.7)	286.1 (171.2)	2.2	97.8	316.2		311.5	
Fish (g/day)	45.2 (74.6)	47.0 (130.9)	38.6	61.4	32.4	0.38	27.5	0.000
Alcohol (g/day)	11.7 (21.3)	6.6 (13.8)	18.8	NLL	18.7	0.10	10.2	0.34
Calcium (mg/day)	1079.7 (480.6)	1138.6 (479.3)	51.7	48.3	865.8	0.004	744.9	0.000
Iron (mg/day)	14.1 (6.8)	14.1 (10.3)	53.8	45.1	12.6	0.13	9.7	0.000
Magnesium (mg/day)	302.3 (136.2)	311.2 (169.5)	26.6	73.4	376.5	0.002	301.9	0.69
Phosphorous (mg/day)	1798.7 (790.5)	1852.1 (1282.9)	84.2	15.8	1653.5	0.13	1284.9	0.000
Potassium (mg/day)	3067.6 (1312.2)	3156.1 (1735.6)	NUL	NLL	3212.3	0.49	2620.0	0.009
Zinc (mg/day)	13.9 (6.4)	14.4 (13.9)	59.8	38.6	12.6	0.19	9.4	0.000
Folate (ug/day)	266.1 (137.7)	276.3 (144.1)	13.6	86.4	307.1	0.09	269.0	0.77
Niacin equivalents (mg/day)	45.9 (2.2)	47.2 (5.1)	94.0	6.0	47.9	0.47	35.0	0.000
Thiamin (mg/day)	1.8 (0.09)	1.8 (1.1)	68.5	29.9	1.8	1.0	1.3	0.001
Vitamin C (mg/day)	112.1 (104.4)	120.0 (108.6)	81.5	18.5	110.1	0.88	94.7	0.06
Vitamin E (mg/day)	6.8 (3.2)	6.4 (3.3)	NUL	NLL	11.3	0.000	9.8	0.005

Note: NLL = no lower limit defined; NUL = no upper limit defined; NR = not recorded.
 * NNS for ages >19 years.
 ** Compared with current population.

significant. Men in the general population consumed more sugar than men with psychosis (115.5 g/day vs 106.9 g/day) whilst women in the general population consumed less sugar than women with psychosis (90.9 g/day vs 105.4 g/day), respectively, but these differences did not reach significance.

Men in the Australian population consumed more carbohydrates (258.8 g/day) compared to men with psychosis (237.0 g/day) and consumed more folate (307.1 g/day) compared to men with psychosis (266.1 g/day). However, consumption of carbohydrates and folate were lower for women in the general population (193.8 g/day and 269.0 g/day) respectively compared to women in the current study (216.9 g/day and 276.3 g/day) respectively, but these differences did not reach significance. The Australian population consumed more fruit and vegetables per day (men: 316.2 g/day, women: 311.5 g/day) in comparison to their male (257.7 g/day) and female (286.1 g/day) counterparts with psychosis.

Overall, the majority of the current sample (51–94%) were likely to be above RDI's for micronutrients, which included: calcium, iron, phosphorous, zinc, niacin, thiamin and vitamin E, whilst a high proportion (73.4% and 86.4%) were below RDI's for magnesium and folate, respectively.

4. Discussion

Our sample had almost twice the proportion of obese patients compared with the Australian population (46.1% vs 24%; Australian Bureau of Statistics, 2007b). In contrast to the general population, a greater proportion of women than men were obese in the psychosis sample. A study assessing dietary intake in schizophrenia found that in comparison to men, women consumed more fruit, vegetables and carbohydrates (McCreadie, 2003). We also know that substance use is higher in men compared to women (Hahn et al., 2014), which may discourage eating behaviour. Levels of physical activity were, very poor as the majority of the sample engaged in low levels of exercise (42%). More subjects were sedentary and fewer performed moderate or vigorous activity compared with the general population (Australian Bureau of Statistics, 2007a). Low participation in physical activity in people with schizophrenia has previously been related to a number of factors including: side-effects of anti-psychotic medication, lower education, lower social support and lower socio-economic status (Vancampfort et al., 2012) all of which are factors common to this survey site in general, and particularly prevalent in people with psychosis living in this region (Hahn et al., 2014).

More than two thirds of our subjects were unemployed so their weekly household income was low. Energy dense, low nutrient foods cost less per megajoule, and so are more likely to be consumed by people with a low household income (Drewnowski & Specter, 2004). Australians who fail to complete year 12 at school are also more likely to be obese (Australian Bureau of Statistics, 2007b). Therefore, socio-demographic factors contribute to our participants' risk of obesity. Our rate of smoking (71%) was similar to published rates in groups of patients with severe mental illness; however, a greater proportion of our female participants smoked than previously described (68.7% vs 56%) (Goff et al., 2005). Hahn et al. (2014) have shown that smoking in women with psychosis is predicted by poor lifestyle habits including alcohol consumption, using cannabis and being sedentary.

Interestingly, alcohol consumption was higher in the general population compared to adults in the current study by 1.1 standard drinks per day (though not significant), which is not consistent with the high prevalence of co-morbid drug use among people with psychosis (Kavanagh et al., 2004). A similar finding to the present study was also observed in a smaller study ($n = 88$) examining alcohol intake among people with schizophrenia (Henderson et al., 2006). This may suggest that people with psychosis cannot afford to consume alcohol, especially if supporting nicotine addiction, unlike adults in the general population who are more likely to be employed.

A quarter of participants in the current study had diabetes and this was much higher than the Australian population (4.4%) (Australian Institute of Health & Welfare, 2011). Diets high in red or processed meat, refined grains, high fat dairy, sweets and desserts were observed in our population and this may have contributed to their high prevalence of diabetes (Alberti et al., 2009). Our subjects also consumed a diet higher in total and saturated fat and lower in fibre than the Australian population. Women consumed more total calories whilst men consumed fewer total calories than the Australian average, and this corresponds with the higher rates of obesity and abdominal obesity observed in our female subjects. This is consistent with the current trend in the Australian population where there is a significant increase in energy consumption by women and a trend towards decreased intake by men (Flood et al., 2010). Similarly, Strassnig et al. (2003) found women with schizophrenia consumed a greater total amount of calories than controls. In contrast, Henderson et al. (2006) found that patients with schizophrenia consumed less total energy than controls, despite having a higher BMI, with a proportional decrease in the contribution of all macronutrients.

The carbohydrate intake of our population was below the RDI. Diets with a lower proportion of carbohydrate can improve BP and triglycerides if replaced by protein or monounsaturated fats (Appel et al., 2005), however in our study, carbohydrate appeared to be substituted for saturated fats, potentially contributing to a worse metabolic profile, which is concerning. Saturated fat is directly proportional to LDL-cholesterol levels and the percentage of saturated fat from dietary calories strongly correlates with coronary death rates (Willett, 2012). Unexpectedly, our population's intake of *trans* fat, which may be more strongly associated with coronary events (Willett, 2012), was within the recommended targets (<1% total energy), despite 44% of subjects consuming sweet biscuits, cakes and pastries, fried or crisp chips, or chocolate on a daily basis.

Our population fell well below the recommended target for fibre, and below the Australian population average (Flood et al., 2010), similar to findings by Strassnig et al. (2003). There is an inverse association between dietary fibre and cardiovascular morbidity and mortality (Liu et al., 2002; Crowe et al., 2012), possibly via lowering LDL-cholesterol levels. Fibre is also linked to improved insulin sensitivity in patients with metabolic syndrome (Johnston et al., 2010). Intervention to improve dietary fibre has not been undertaken in people with psychosis, though it is certainly plausible that such an intervention would have metabolic benefits.

Intake of fruit and vegetables by our subjects was very poor which is consistent with previous research (McCreadie, 2003). However, whilst our population failed to meet RDIs, this is similar to the general Australian population where only 6% consume two serves of fruit and five serves of vegetables per day (McLennan and Podger, 1997). Fruit and vegetables lower blood pressure and improve cholesterol profiles (Obarzanek et al., 2001). Interventions to improve the diet of people with schizophrenia found that providing free fruit and vegetables doubled the intake of these foods, however, the improvement only lasted the duration of the trial (McCreadie et al., 2005). Education and support did not offer any additional benefit and there was no change in the cardiovascular risk of these patients at any time point.

High sodium and low potassium consumption increase the risk of hypertension (Sacks et al., 2001; Geleijnse et al., 2003) and large intakes of sodium were observed in the present study. The current trend in Australia is an increase in sodium intake and our average was higher than intakes recorded in 2004 (3256.4 vs 2086–2304 mg/day; Flood et al., 2010). Our male subjects consumed less and our female subjects consumed more potassium than Australian controls. However, our population generally had low sodium:potassium ratios (M = 1.03, SD = 0.34) which is associated with a lower cardiovascular risk (Yang et al., 2011).

The average intake of fish in the Australian diet has increased over the last two decades (Flood et al., 2010; Kolahdooz et al., 2010).

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However, 46% of the Australian population still consume less than the recommended guideline of two serves of fish/week (Kolahdooz et al., 2010). Our population had a skewed distribution of fish intake (mean: 46.0 g/day, median: 22.6 g/day, range: 0–1162.7,) with most people reporting that they never consumed fish. Nonetheless, 26.9% of participants consumed >500 mg of DHA + EPA per day, as recommended for primary prevention of coronary heart disease (National Heart Foundation of Australia, 1999). The average intake of long chain fatty acids in our subjects remains higher than the Australian population (0.47 g vs 0.3 g/day; Flood et al., 2010), potentially providing some benefit. Interestingly, women with psychosis did better in terms of vitamin and mineral daily intake, as they consumed more iron, phosphorous, potassium, zinc, niacin equivalents, and thiamin compared to women in the Australian population. They also had higher intakes of energy, protein, mono-saturated fat, poly-unsaturated fat and fish compared to the reference population, and foods rich in these nutrients are also rich in vitamins and minerals, which may support this finding.

4.1. Limitations

A clear limitation is the relatively small sample size that resulted from unwillingness to complete the assessments or patients being unreachable. This study was a cross-sectional design, thus, limiting our findings. The majority of participants were taking anti-psychotic medication which has previously shown to increase food cravings for sweet and fatty foods and promote binge eating behaviour (Kluge et al., 2007). We did not have a control sample matched for BMI, age, sex and educational status which limits the generalizability of the results. The DQES is retrospective in contrast to having a real life assessment over time which would provide more accurate results. Up to one third of patients may under-report their dietary intake. This has been linked with lower fat and micronutrient intakes (Livingstone & Black, 2003), characteristics that were not found in our study, arguing against under-reporting. The DQES has not been validated in people with psychosis.

The range and standard deviation of many of the nutritional variables was large compared with control populations. This could reflect the nature of the DQES itself or possibly the difference in dietary intake between subgroups of participants. Previous authors have also found great variability in intake of patients with severe mental illness (Strassnig et al., 2003; Henderson et al., 2006).

4.2. Conclusions

We found that the diets of patients with psychosis are not consistent with those recommended to reduce cardiovascular disease, thus putting this group at higher CVD risk. This is particularly seen in women, though the higher intake of daily vitamins and minerals among women with psychosis and lower consumption of alcohol, compared to our comparison data appears contradictory. Despite higher intake of micro-nutrients compared to the Australian population, the consumption of fats, sodium and carbohydrates, all of which contribute to cardiovascular disease was high in our sample. Other factors including smoking, sedentary lifestyle, medication and under-treatment of comorbidities are also likely to contribute to the heightened cardiovascular risk in this population.

Contributors

All authors contributed to the design of the study and protocol. Marni Nenke and Lisa Hahn conducted the literature review and undertook statistical analyses. All authors commented on the first manuscript and contributed to the writing of subsequent versions. All authors approved the final manuscript.

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CHAPTER 5: Paper 3

Statement of Authorship

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Contribution to the Paper	Undertook the literature review, conducted data analysis, interpreted data, drafted and prepared manuscript, and submitted manuscript to journal.		
Overall percentage (%)	60%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

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ii. permission is granted for the candidate in include the publication in the thesis; and
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Objective
Hypertension is one of the most important risk factors for cardiovascular disease (CVD). Systolic and diastolic blood pressure (BP) is higher in people with psychosis but there is little research into measures of the elasticity of the arterial wall (pulse pressure; PP) and peripheral resistance (mean arterial pressure; MAP). PP and MAP can provide an additional perspective on the functioning of the circulatory system. This study investigated PP and MAP in people with psychosis, using factors known to be related to PP and MAP in the general population.

Method
Participants included 1421 people aged 18-64 years, from the second Australian national survey of psychosis, untreated with antihypertensive medication. We tested the interaction and main effects between age and gender on PP, MAP, systolic BP and diastolic BP. Odds ratios were calculated in people exceeding the at-risk thresholds for PP and MAP. Multiple linear regression was used to determine risk factors associated with PP and MAP.

Results
The interaction effect between age and gender on PP, MAP, systolic BP and diastolic BP was not statistically significant. After adjustment for age, gender and all other factors, variables that retained significance in the regression model in explaining higher PP and MAP were: male gender, higher age, and having a family history of hypertension.

Conclusion
Clinicians monitoring and treating CV risk in this population need to ensure that they have recorded whether there is a family history of hypertension, and should be especially, more vigilant in men and in older patients.

1. Introduction

Hypertension is the second leading global risk factor for cardiovascular disease (World Health Organisation, 2009). It has been called "the silent killer" as it is often unrecognised and untreated (WHO, 2009). Worldwide, hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke. Detection of hypertension is important as effective treatments are available and, even in mild hypertension, are associated with reduced CV morbidity and mortality (Sundstrom et al., 2015).

Two components of blood pressure (BP) are commonly measured. Systolic BP measures the pressure in the arteries when the heart contracts and diastolic BP measures arterial pressure while the heart is at rest between contractions. Pulse pressure (PP) is calculated as the difference between systolic and diastolic BP. Elevated PP indicates stiffness (lack of normal elasticity) in the arterial walls. PP is recognized as an independent contributor to CVD risk in middle-aged and older individuals (Staessen et al., 2000). Elevated PP is associated with severe atherosclerosis (Lyon et al., 1987) rupture of arteriosclerotic plaques (Cheng et al., 1993), carotid artery disease (Mancia et al., 2001) and small-vessel disease (van Sloten et al., 2015). Usually, the resting pulse pressure in healthy adults is about 30-40 mmHg. A resting pulse pressure greater than 60 mmHg is associated with increased cardiovascular morbidity and mortality (Blacher et al., 2000; Panagiotakos et al., 2005).

Mean arterial pressure (MAP) is defined as the average pressure in a person's arteries during one cardiac cycle. MAP reflects cardiac output and peripheral resistance and is considered a better indicator of perfusion to vital organs than systolic blood pressure (Tyrovolas et al., 2014). MAP is measured as 1/3 systolic BP + 2/3 diastolic BP. The diastolic value is weighted doubly because the diastolic portion of the cardiac cycle is typically twice as long as the systolic. A MAP between 70-100 mm Hg is considered to be within the normal range. A MAP value $\geq$ 97 mm Hg is associated with a relative risk for CVD of 2.52 among men aged less than 60 years old (Sesso et al., 2000). In middle aged men aged 30-45 years, a higher MAP predicted CVD mortality with a relative risk of 1.48, independent of age, BMI and serum cholesterol concentration (Strandberg et al., 2002).

Research examining associations of blood pressure generally use a definition of hypertension based on elevation of either systolic or diastolic BP. Less is known about the risks that may be revealed by elevated PP or MAP values. Gu et al. (2010) found that among hypertensive adults aged 18 years and over in the general population, the risk of all-cause mortality and CV mortality progressively increased with each 10 mm Hg increment in SBP, PP or MAP; diastolic BP did not predict CV mortality. Tyrovolas et al. (2014) reported that a higher PP was associated with diabetes, obesity, and living alone; while physical activity and higher education were negatively associated with PP. Obesity was linked with higher MAP, while greater adherence to a Mediterranean diet was protective against increasing MAP. Unexpectedly, higher financial status was associated with elevated PP and MAP.

There has been very little research reporting PP and MAP in people with psychosis. Fernandez-Egea et al (2009) found that 41 young people with first episode psychosis had a higher mean PP, compared to matched controls (47.9 (9.3) vs 41.8 (8.8) mm Hg). In a pilot study assessing arterial stiffness in a sample of 10 people with schizophrenia-spectrum disorders, MAP was higher compared to 10 matched controls (89 (17) mm Hg vs 83 (8) mm Hg) but this difference was not significant (Phillips et al., 2014). These studies were limited

by small sample sizes. Hence, there is a need to examine PP and MAP in a much larger sample of people with psychosis.

In our previous work with the current cohort, we found that of 1766 people with psychosis aged 18-64 years, including both individuals treated and untreated with antihypertensive medication, 29.9% had systolic hypertension (systolic BP $\geq$ 130 mm Hg) and 42.3% had diastolic hypertension (diastolic BP $\geq$ 85 mm Hg). Hypertension was more common in men and in older participants. Overall, 19.8% reported that they had been diagnosed with hypertension, and just over half (51.7%) of these participants were taking antihypertensive medication (Galletly et al., 2012). Diastolic hypertension was more prevalent in people with psychosis compared with the general population, but systolic hypertension was lower in people with psychosis compared with the general population (Foley et al., 2013).

These results suggest a difference in the pattern of hypertension in people with psychosis, which we aimed to investigate further by using other measures of BP in this population. The current study investigated whether factors shown to predict higher PP and MAP in the general population were also associated with elevated PP and MAP in people with psychosis.

2. Methods:

2.1 Study population

Data from 1825 participants with psychosis aged 18-64 years were collected during the second Australian national survey of people living with psychosis (2010). A detailed description of the method has been published previously (Morgan et al., 2014). The study consisted of a two-phase sampling design: In phase 1, people aged 18-64 years and in contact with public mental health services and non-government organisations in the previous 12 months were screened for psychosis. A total of 1825 people who were screen positive for psychosis in phase 1 (n = 7955) were randomly chosen during phase 2 for interview and assessment which included fasting blood tests and blood pressure, waist, height and weight measurements.

Participants were diagnosed according to the International Classification of Disease 10th revision (ICD-10) (World Health Organization, 1992) using the diagnostic interview for psychosis (Castle et al., 2006), resulting in a total of 1642 participants diagnosed with affective psychosis and non-affective psychosis. PP and MAP were obtained from 1590 of these participants. Participants currently taking antihypertensive medication (n = 169) were excluded from this analysis. Of the remaining 1421 participants who were untreated with antihypertensive medication, 1029 provided a fasting blood sample. There was no difference between participants who gave fasting blood samples and those who did not in terms of age group, gender, BMI, waist circumference, level of education, school-leaving age or lifetime smoking.

All participants provided written, informed consent. The study was approved by institutional human research ethics committees at each of the seven study sites.

2.2 Data collection and assessment

Demographic and clinical factors were assessed. Participants were divided into three age groups: younger age (18-29 years); middle age (30-44 years) and older age (45-64 years).

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Socio-economic status was assessed at postcode level using the Index of Relative Socio-Economic Disadvantage (Australian Bureau of Statistics, 2006). Participants were asked to bring all currently prescribed medications to the interview. Participants were asked to fast for blood tests (a minimum of eight hours) for analysis of plasma cholesterol, triglyceride and glucose levels.

Participants were seated for at least 5-10 minutes before BP measurement. A digital blood pressure monitor, manufactured by A&D Company Ltd, model UA-767 Plus, was used to record blood pressure readings. These readings were used as a continuous variable and were recoded into a binary variable to reflect if hypertension was present (yes vs no). Hypertension was diagnosed according to guidelines from the 2013 European Society of Hypertension and the European Society of Cardiology Task Force for the Management of Arterial Hypertension (Mancia et al., 2013). The cut off criteria was systolic $\geq$140 mm Hg and/or diastolic $\geq$90 mm Hg.

Pulse pressure was derived by subtracting diastolic blood pressure from systolic blood pressure. A cut off criteria of >60 mm Hg was taken to indicate high PP (Panagiotakos et al., 2005). Mean arterial pressure was also derived: MAP = (systolic + 2×diastolic)/3. A value of MAP $\geq$97 mm Hg was taken to indicate abnormal elevation of MAP (Sesso et al., 2000).

Excessive alcohol consumption reflected an average daily consumption of four or more standard drinks per day, four or more times per week in the past year. Participants were classified as current smokers if they had smoked tobacco in the previous 4 weeks. Physical activity was evaluated using the International Physical Activity Questionnaire (short form), with three physical activity level categories: high, moderate and low (Craig et al., 2003).

Inadequate diet was based on Australian guidelines and was defined by the number of servings of fruit and vegetables consumed daily in the past week. Consuming fewer than 5 servings of vegetables and fewer than 2 servings of fruit daily, was coded as having an inadequate intake (National Health and Medical Research Council, 2006).

Pre-diabetes and type 2 diabetes were categorised according to the American Diabetes Association criteria of a fasting blood glucose level of 5-6-6.9 mmol/L and $\geq$ 7 mmol/L, respectively (American Diabetes Association, 2008). Euglycaemia was defined as a fasting blood glucose < 5.6 mmol/L. A value $\geq$4 mmol/l indicated high LDL cholesterol. Body mass index (BMI) was calculated as weight/height^2 (World Health Organisation, 2009). Participants were categorised as normal or underweight (BMI <25), overweight (BMI 25-29.9), or classified into three obesity categories: class 1 (BMI 30-34.9), class 2 (BMI 35-39.9) and class 3 (BMI $\geq$40). Participants were asked if they had a family history of high blood pressure in first degree relatives.

2.3 Data analysis

Statistical analyses were performed using SPSS (version 21; IBM Corp 2012). Preliminary tests were conducted using independent sample-t-tests and a one-way analysis of variance (ANOVA) to identify associations between various risk factor variables (independent variable) and PP and MAP (dependent variable). Variables that were previously associated with PP and MAP in the general population from research literature were tested in this current sample of people with psychosis. Factors that were significantly related with PP or MAP in the univariate model were further entered into a regression model.

A two-way analysis of variance (ANOVA) assessed the main and interaction effects of age and gender on continuous blood pressure outcomes (systolic BP, diastolic BP, PP and MAP). This test was adjusted for age and gender, because in our previous work, there were significant differences for systolic hypertension and diastolic hypertension between men and women. Potential significant main effects were further explored using Tukey post-hoc tests. Logistic regression was used to determine the association between dichotomised indicators of clinically elevated blood pressure and various risk factors and their interactions.

Multiple linear regression investigated the association between PP and MAP (dependent variables), and potential|established|putiative risk factors (gender, age, marital status, unemployment, living status, BMI, alcohol and tobacco use, diastolic BP, family history of hypertension, cholesterol levels and physical activity) (independent variables). The associations of the independent variables with PP and MAP were adjusted for age and gender in the first stage of modelling and then were adjusted for age, gender, diastolic blood pressure and all other factors in a second stage. Results are presented as unstandardised regression coefficients (β) with their corresponding 95% confidence intervals.

3. Results

Mean comparisons of blood pressure components

Table 1 presents characteristics of the total sample of people with psychosis.

The interaction effect between gender and age group for all four blood pressure indices (systolic BP, diastolic BP, PP and MAP) was not statistically significant and did not make a difference in improving the model (Table 2). There was a statistically significant main effect for gender. Men had higher systolic BP, pulse pressure and MAP compared to women. There was a statistically, significant main effect for age. Post-hoc comparisons showed that mean systolic BP and mean diastolic BP was higher in people aged 45-64 years compared with the younger age groups; diastolic BP was higher in people aged 30-44 years compared with people aged 18-29 years. Pulse pressure was higher in people aged 45-64 years compared with middle aged people; PP was higher in people aged 18-29 years than the middle age group; MAP was higher in people aged 45-64 and 39-44 years compared to the younger age groups.

Predictors of exceeding at-risk thresholds for blood pressure components

The interaction effect between gender and age group was not statistically significant for the various blood pressure components (Table 3). There was a statistically significant main effect for age and gender. Male gender significantly increased the risk of diastolic hypertension (OR 1.97, 95% CI: 1.02 – 3.79), above at-risk threshold PP (OR 7.63, CI: 1.10 – 58.44) and above at-risk threshold MAP (OR 1.98, 95% CI: 1.22 – 3.22). Middle age (30-44 years) significantly increased the risk of diastolic hypertension (OR 2.89, 95% CI: 1.52 – 5.48) and above at-risk threshold MAP (OR 2.05, 95% CI: 1.26 – 3.32). Older age (45-64 years) significantly increased the risk of systolic hypertension (OR 6.16, 95% CI: 2.10 – 18.06), diastolic hypertension (OR 4.31, 95% CI: 2.23 – 8.36) and above at-risk threshold MAP (OR 3.32, 95% CI: 1.98 – 5.56).

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Factors associated with pulse pressure and mean arterial pressure

Table 4 shows univariate associations of risk factor variables with PP and MAP. After the variables from Table 4 were entered into the regression analysis (Table 5) adjusted for age and gender, PP was significantly higher in relation to male gender (β: 5.78, CI: 4.50 – 7.05) and having a family history of hypertension (β: 1.71, CI: 0.39 – 3.02); BMI and diastolic BP were inversely associated with PP. Adjusting for age and gender, MAP significantly increased in relation to male gender (β: 2.66, CI:1.42 – 3.90), higher age (β: 0.22, CI: 0.17 – 0.28), unemployment (β: 1.76, CI: 0.31 – 3.21), higher BMI (β: 0.53, CI: 0.45 – 0.61), having a family history of hypertension (β: 2.65, CI: 1.38 – 3.92); while having a single, separated or divorced marital status was inversely related with MAP (Table 5).

When the model was adjusted for age, gender and all other factors, variables that retained significance with PP and MAP were male gender, higher age and having a family history of hypertension.

Associations of pulse pressure and mean arterial pressure with diastolic BP

In the model adjusted for age and gender only, diastolic BP was inversely associated with PP; diastolic BP was positively associated with MAP. Adjusting for age, gender and all other factors, the relationship between diastolic BP with PP and MAP retained significance.

Table1. Characteristics of people with psychosis not treated with antihypertensive medications.

Characteristics	n =1421	% or M(SD)
Sex		
Male	887	62.4
Female	534	37.6
Mean age (years)	1421	37.07 (10.58)
Age (years)		
18-34	654	46.0
35-64	767	54.0
Marital status		
Single, never married	915	64.4
Married or defacto	230	16.2
Separated, divorced or widowed	276	19.4
Lives alone	405/1391	29.1
Fortnightly income		
<$300	50/1343	3.7
$300-499	168/1343	12.5
$500-799	823/1343	61.3
$800-10000	197/1343	14.7
>$1000	105/1343	7.8
Body Mass Index (BMI)	1410	30.09 (7.21)
Fasting plasma glucose level (mmol/l)	1093	5.36 (1.10)
High LDL cholesterol (> 4 mmol/l)	159/1408	11.3
Family history of hypertension in first degree relatives		
No	759/1280	59.3
Yes	521/1280	40.7

Table 1. Continued

Education		
Left school with no qualifications	476/1410	33.8
Secondary school qualification	243/1410	17.2
Tertiary/other	691/1410	49.0
Enrolled in formal study (past year)	293	20.6
Unemployed (last 7 days)	1109	78.0
Index of relative socio-economic disadvantage (IRSD): 1-2 = deciles of greatest socio-economic disadvantage	294	20.7
IRSD: 3-4	315	22.2
IRSD: 4-6	413	29.1
IRSD: 7-8	228	16.1
IRSD: 9-10 = deciles of least socio-economic disadvantage	170	12.0
ICD-10 Diagnosis		
Non-affective psychosis		
Schizophrenia	759	53.4
Schizoaffective disorder	249	17.5
Delusional disorders and other non-organic psychoses	77	5.4
Affective psychosis		
Bipolar disorder with psychotic features	270	19.0
Depressive psychosis	66	4.6
Alcohol risk		
Low	957	67.3
Hazardous	271	19.1
Harmful/dependent	193	13.6
Current smoker	979	69.3
Inadequate diet		
No	81/1414	5.7
Yes	1333/1414	94.3
Physical activity		
High	212/1406	15.1
Moderate	541/1406	38.5
Low	653/1406	46.4

Table 2. Mean systolic and diastolic blood pressure, pulse pressure and mean arterial pressure in people with psychosis.

	Men	Women	p value	Age 18-29 years	Age 30-44 years	Age 45-64 years	Total	p value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Systolic BP	123.94 (15.52)	117.95 (15.35)	<0.0001	119.14 (14.25)	121.24 (15.02)	125.13 (17.74)	121.69 (15.72)	<0.0001[a,b]
Diastolic BP	82.43 (11.56)	82.12 (11.56)	0.356	78.89 (11.02)	83.06 (11.40)	84.36 (11.61)	82.31 (11.56)	<0.0001[a,c]
Pulse pressure	41.51 (12.07)	35.83 (11.38)	<0.0001	40.25 (12.16)	38.18 (11.31)	40.77 (13.33)	39.38 (12.13)	<0.0001[b,c]
MAP	96.27 (11.70)	94.06 (11.78)	<0.0001	92.30 (10.80)	95.79 (11.55)	97.95 (12.46)	95.44 (11.78)	<0.0001[a,b,c]

[a]Significant comparisons between 18-29 years and 45-64 years age groups.
[b]Significant comparisons between 30-44 years and 45-64 years age groups.
[c]Significant comparison between 18-29 years and 30-44 years age groups.

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Table 3. Main effects and Interaction effects of age and gender in predicting above at-risk threshold systolic and diastolic blood pressure, pulse pressure and mean arterial pressure.

	Systolic hypertension (BP ≥140 mm Hg)		Diastolic hypertension BP ≥ 90 mm Hg)		PP > 60 mm Hg		MAP ≥ 97 mm Hg	
	n (%)	Adjusted OR (95% CI)	n (%)	Adjusted OR (95% CI)	n (%)	Adjusted OR (95% CI)	n (%)	Adjusted OR (95% CI)
Gender								
Female	47 (8.8%)	Reference group	134 (25.1%)	Reference group	12 (2.2%)	Reference group	217 (40.6%)	Reference group
Male	125 (14.1%)	2.53 (0.85 – 7.58)	242 (27.3%)	1.97 (1.02 – 3.79)*	64 (6.1%)	7.63 (1.01 –58.44)*	439 (49.5%)	1.98 (1.22 – 3.22)**
Age group								
18-29 years	24 (6.5%)	Reference group	61 (16.5%)	Reference group	16 (4.3%)	Reference group	129 (35.0%)	Reference group
30-44 years	75 (10.9%)	1.82 (0.59 – 5.61)	192 (27.9%)	2.89 (1.52 – 5.48)**	22 (3.2%)	0.94 (0.09 – 10.52)	328 (47.7%)	2.05 (1.26 – 3.32)**
45-64 years	73 (20.0%)	6.15 (2.10 – 18.06)**	123 (33.7%)	4.31 (2.23 –8.36)***	28 (7.7%)	7.09 (0.89 – 56.77)	199 (55.4%)	3.32 (1.98 –5.56)***
Interaction terms								
18-29 years x female	4 (3.3%)	Reference group	13 (10.8%)	Reference group	1 (0.8%)	Reference group	30 (25.0%)	Reference group
30-44 years x male gender	60 (13.9%)	1.01 (0.29 – 3.51)	126 (29.1%)	0.61 (0.28 – 1.25)	20 (4.6%)	0.80 (0.07 – 9.81)	225 (52.0%)	0.80 (0.45 – 1.43)
45-64 years x male gender	45 (22.2%)	0.52 (0.16 – 1.77)	68 (33.2%)	0.48 (0.22 – 1.06)	19 (9.3%)	0.23 (0.03 – 2.02)	115 (56.1%)	0.58 (0.31 – 1.11)

*p< 0.05; **p<0.01; ***p<0.0001.

Table 4. Associations of established risk factor variables with pulse pressure (PP) and mean arterial pressure (MAP).

Risk Factors	PP (n =1421)	Test	MAP (n =1421)	Test
	Mean (SD)		Mean (SD)	
Sex				
Male	41.51 (12.07)	$t(1419) = 8.78, p < 0.0001$	96.27 (11.70)	$t(1419)=6.77, p < 0.0001$
Female	35.83 (11.38)		94.06 (11.78)	
Age group(years)				
18-29	40.25 (12.16)	$F(2, 1418) = 6.78, p < 0.01^a$	92.30 (10.80)	$F(2, 1418) = 22.31, p < 0.0001^b$
30-34	38.17 (11.31)		95.79 (11.55)	
45-64	40.77 (13.33)		97.95 (12.46)	
ICD-10 Diagnosis				
Non-affective psychosis	39.49 (12.10)	$t(1419) = -0.65, p = 0.519$	95.16 (11.84)	$t(1419) = 1.60, p = 0.110$
Affective psychosis	39.01 (12.24)		96.34 (11.55)	
Marital status				
Single, never married	39.37 (12.28)	$F(2, 1418) = 0.00, p = 0.999$	94.28 (11.74)	$F(2, 1418) = 14.98, p < 0.0001^c$
Married or Defacto	39.41 (12.18)		96.33 (11.40)	
Separated, divorced or widowed	39.39 (11.62)		98.54 (11.62)	
Education status				
Left school with no qualifications	38.78 (12.68)	$F(2, 1407) = 1.22, p = 0.295$	95.84 (12.54)	$F(2, 1407) = 1.04, p = 0.353$
Secondary school qualification	40.27 (12.12)		95.93 (10.72)	
Tertiary/other[d]	39.41 (11.77)		94.97 (11.60)	

Table 4. Continued

Unemployed (last 4 weeks)				
No	39.18 (12.03)	$t(1419) = -1.15, p = 0.250$	93.66 (10.66)	$t(1419) = 3.02, p < 0.01$
Yes	40.08 (12.47)		95.94 (12.03)	
Living alone				
No	39.48 (12.25)	$t(1389) = 0.11, p = 0.915$	95.03 (11.73)	$t(1389) = -2.30, p < 0.05$
Yes	39.40 (12.08)		96.63 (11.86)	
Income				
<$300	40.64 (12.60)	$F(3, 1417) = 1.23, p = 0.299$	93.97 (12.64)	$F(3, 1417) = 1.91, p = 0.127$
$300-499	40.54 (12.88)		94.03 (12.71)	
$500-799	39.07 (12.25)		95.90 (11.72)	
$800 or more	39.04 (11.11)		95.59-10.94	
Current smoker				
No	38.42 (12.49)	$t(1410) = -1.94, p < 0.05$	95.26 (11.92)	$t(1410) = -0.29, p = 0.773$
Yes	39.78 (11.99)		95.45 (11.69)	
Alcohol risk				
No	39.19 (12.18)	$t(1413) = -2.01, p < 0.05$	95.18 (11.62)	$t(1413) = -2.01, p < 0.05$
Yes	41.50 (11.67)		97.68 (13.16)	
BMI				
Normal (18.5-24.9)	39.95 (11.57)*	$F(4, 1416) = 4.83, p < 0.01^{e}$	90.19 (10.95)*	$F(4, 1416) = 32.41, p < 0.0001^{f}$
Overweight (25-29.9)	40.44 (12.33)		94.51 (11.66)*	
Obese, class 1 (30-34.9)	39.94 (12.42)		98.21 (11.29)*	
Obese, class 2 (35-39.9)	36.43 (11.67)		98.51 (9.83)*	
Obese, class 3 ($\geq$ 40)	37.35 (12.01)*		99.64 (12.23)*	

Table 4. Continued

Diabetes risk				
Euglycaemia (< 5.6 mmol/l)	39.63 (11.80)	$F(2, 1418) = 1.26$, $p = 0.285$	94.92 (11.85)	$F(2, 1418) = 6.81$, $p < 0.01^g$
Pre-diabetes (5.6-6.9 mmol/l)	38.25 (13.94)		98.16 (11.30)	
Type 2 diabetes(≥7 mmol/l)	38.81 (11.48)		95.45 (11.10)	
High LDL cholesterol >4 mmol/l				
No	39.57 (12.16)	$t(1406) = 1.51$, $p = 0.131$	95.15 (11.76)	$t(1406) = -2.02$, $p < 0.05$
Yes	38.03 (11.50)		97.14 (11.48)	
Family history of hypertension				
No	38.86 (11.56)	$t(1278) = -1.72$, $p = 0.091$	94.31 (11.27)	$t(1278) = -3.87$, $p < 0.0001$
Yes	40.04 (12.73)		96.87 (12.09)	
Inadequate Diet				
No	39.21 (13.17)	$t(1412) = -0.13$, $p = 0.896$	96.21 (12.71)	$t(1412) = 0.63$, $p = 0.529$
Yes	39.39 (12.08)		95.36 (11.70)	
Physical activity				
High	41.19 (11.85)	$F(2,1403)= 2.94$, $p < 0.05^h$	94.98 (10.48)	$F(2, 1403) = 0.34$, $p = 0.715$
Moderate	39.18 (12.51)		95.34 (11.93)	
Low	38.92 (11.77)		95.70 (12.00)	

[a]Pulse pressure (PP) in the 18-29 years age group is significantly different from the 30-44 years age group; and PP in the 30-44 years age group is significantly different from the 45-64 years age group; [b]Mean arterial pressure (MAP) is significantly different in the 18-29 years age group from the 30-44 years age group; MAP is significantly different in the 45-64 years age group from the 18-29 years age group; MAP is significantly different in the 30-44 years age group from the 45-64 years age group. [c]MAP is significantly different in people with a single, never married marital status from people with a currently married or defacto marital status; MAP is significantly different in people with a currently separated, divorced or widowed marital status from people with a single, never married, marital status. [d]Other includes TAFE, trade or diploma qualification; [e]PP significantly different in people with normal weight from people with class II obesity; PP significantly different in people who are overweight from people with class II-III obesity; PP significantly different in people with class I obesity from people with class II obesity; [f]MAP is significantly different in people with normal weight from people who are overweight and have class I-III obesity; MAP is significantly different in people who are overweight from people with normal weight and class I-III obesity; [g]MAP is significantly different in people with euglycemia from people with pre-diabetes; [h]PP is significantly different in the high physical activity group from the low physical activity group.

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4. Discussion

We found that people with psychosis who were older aged and male were more likely to have a higher MAP compared with people who were younger or female. Higher MAP indicates greater peripheral resistance, which may adversely affect the diameter of vessels and lead to inadequate perfusion of the vascular network (McGhee and Bridges, 2002, Henry et al., 2002). In our cohort, older men (45-64 years) had a higher mean PP compared with middle aged men (30-44 years), but younger men (18-29 years) had a higher mean PP (40.25, SD: 12.16) compared with middle aged men (38.18, SD: 11.31). In line with this finding, there is some evidence from general population studies, that the trajectory of pulse pressure with age in men is U-shaped From age 20, mean PP trends downwards through to middle age then begins to steadily increase with age (Skurnick et al., 2010). These results in the general population suggest that the pattern of PP in young men with psychosis may not be that different to the pattern of PP among young men in the normal population.

We have shown previously that, compared with the general population, people with psychosis are more likely to have elevated diastolic than systolic BP (Foley et al., 2013). Only 6.1% of men and 2.2% of women exceeded the at-risk threshold for PP, representing a much smaller proportion than those meeting the criteria for at-risk systolic or diastolic BP or MAP. In contrast to PP, MAP exceeded the at-risk threshold in almost half (49.5%) of male participants and 40.6% of women. This may reflect the formula used to calculate MAP. Diastolic BP (which tends to be elevated) is doubled, thus, diastolic BP contributes twice as much as systolic BP to the MAP.

Our findings from the univariate associations with PP and MAP are consistent with factors known to contribute to arterial damage in the general population (Lee et al., 2005). Poor lifestyle factors characterised by smoking, excessive alcohol intake and unemployment increased PP and MAP in our sample. People who lived alone or were separated, divorced or widowed had a higher MAP compared to people who lived with others or had a single marital status. It is likely this finding represents the life course of age. Mean arterial pressure increased in each obesity category, but the association between PP and obesity was non-linear. Biomedical risks including high LDL cholesterol and pre-diabetes were associated with increased MAP. Possible mechanisms by which these risks affect peripheral resistance may involve activation of the sympathetic nervous system and systemic inflammatory molecules or leptin levels (Poirier et al., 2006). Generally, higher levels of physical activity decreases PP (Seals et al., 2009) but we did not find this in our current study as people who engaged in the highest levels of exercise had the highest mean PP. People who were younger or middle aged in this study were more likely to participate in high levels of physical activity compared to people who were older aged.

Findings from the regression analysis revealed that male gender had the strongest association with increasing PP and increasing MAP, after adjustment for all other factors. A family history of hypertension and old age also increased the risk of having elevated PP and MAP. Higher diastolic BP increased the risk of elevated MAP. The only factor in common that was related to PP and MAP in both our study and the general population was obesity (Tyrovolas et al., 2014), but this lost significance after the model was adjusted for all subsequent factors.

This study has several limitations, including the cross sectional study design. Mean arterial pressure and PP do not represent direct measures of peripheral resistance and aortic stiffness. A full haemodynamic analysis assessing microcirculatory blood flow, pulse wave velocity,

diastolic pulse waveform analysis, central aortic pressure, ambulatory blood pressure monitoring and heart rate variability, is required to fully understand the blood pressure profile among people with psychosis.

4.2 Conclusions

In conclusion, this study provides new information about measures of arterial elasticity and peripheral resistance in people with psychosis. Older men in particular seem to be at a greater risk. A family history of hypertension appears to play a strong role in the elevation of PP and MAP. Unmodifiable factors such as age, gender and hereditary appear to more related to poorer PP and MAP compared with modifiable factors, in this cohort of people with psychosis. This study showed that older men with a family history of hypertension represent an important target group for intervention to lower PP and MAP and ultimately reduce the risk of CVD.

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SECTION B

Total Number of Risk Factors Present

Statement of Authorship

Title of Paper	Counting up the risk factors for morbidity and mortality in young people with psychosis.
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Lisa Hahn		
Contribution to the Paper	Conducted the literature review, performed data analysis, interpreted data, drafted manuscript, prepared manuscript for journal submission and submitted manuscript to journal.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	08.03.2016

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

    i.   the candidate's stated contribution to the publication is accurate (as detailed above);

    ii.   permission is granted for the candidate in include the publication in the thesis; and

    iii.   the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Andrew Mackinnon		
Contribution to the Paper	Commented and edited drafts of manuscript, advised on analytic strategy, statistical procedures and interpretation of results.		
Signature		Date	10.03.2016

Name of Co-Author	Debra Foley		
Contribution to the Paper	Commented and edited drafts of manuscript, picked up errors in the handling of data, errors in the interpretation of data analyses, inconsistencies in the reporting of findings, errors in the interpretation of previously published work and advised on how to write and structure a paper.		
Signature		Date	09.05.2016

Name of Co-Author	Vera Morgan		
Contribution to the Paper	Commented and edited drafts of manuscripts and made suggestions on the presentation of material in the paper, advised on how to handle data in SPSS.		
Signature		Date	04.05.2016

Name of Co-Author	Anna Waterreus		
Contribution to the Paper	Commented and edited drafts of manuscripts and made suggestions on the presentation of material in the paper.		
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Contribution to the Paper	Commented and edited drafts of manuscripts and made suggestions on the presentation of material in the paper.		
Signature		Date	07.03.2016

Name of Co-Author	David Castle		
Contribution to the Paper	Commented and edited drafts of manuscripts and made suggestions on the presentation of material in the paper.		
Signature		Date	08.03.2016

Name of Co-Author	Dennis Liu		
Contribution to the Paper	Commented on drafts and provided feedback.		
Signature		Date	08.03.2016

Name of Co-Author	Cherrie Galletly		
Contribution to the Paper	Commented and edited drafts of manuscripts, made suggestions on the presentation of material in the paper, incorporated changes into the draft, suggested journal for manuscript submission.		
Signature		Date	08.03.2016

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Aim

This study examined the prevalence of risk factors for cardiovascular (CV) related morbidity and mortality in young people with psychosis aged 18-24 years.

Methods

The study included 132 people aged 18-24 years who participated in the 2010 second Australian national survey of people living with psychosis. The 2009 World Health Organisation (WHO) Global Health Risks report was used as a framework to determine which specific risk factors were present in each in these young people. The risk factors assessed in this study were smoking, alcohol use, hypertension, overweight/obesity, physical inactivity, high blood glucose, high cholesterol and poor diet. Each risk factor was defined according to WHO criteria. A count of the total number of risk factors present for each participant was determined. Data for male and female participants was compared.

Results

Young men had an average of 2.9 (SD 1.2) risk factors. Young women had an average of 2.4 (SD 1.2) risk factors. The most common risk factors were low fruit and vegetable intake (77.9%), cigarette smoking (67.7%), overweight/obesity (55%) and physical inactivity (39.8%). There were no significant differences between men and women in the number of risk factors present, or the prevalence of individual risk factors.

Conclusion

This study demonstrated that many of the risk factors that ultimately contribute to disability and premature death are present at an early age in people with psychosis. Preventive measures need to be an integral component of early intervention services for this client population to avert progression to serious cardiovascular morbidity and early mortality.

Key words: Morbidity, Mortality, Risk Factors, Cardiovascular Disease, Young Psychosis, World Health Organisation.

Introduction

There has been increasing recognition of the poor physical health and reduced life expectancy of people with chronic psychiatric disorders such as schizophrenia and bipolar disorder[1, 2, 3]. A 10 year follow-up study of people presenting with first episode psychosis (FEP) found a standardized mortality ratio (SMR) of 3.6[4]. Similarly, Dutta et al (2012) reported that in the UK, people with FEP have an overall mortality risk nearly double that of the general population. Most of these deaths are due to cardiovascular (CV) disease (Laursen et al., 2013), leading researchers to question why people with psychosis have a higher prevalence of CV disease, and why this CV disease progresses to death at an earlier age, compared with the general population.

The Framingham study, along with other large cohort studies, has led to the identification of CV risk factors, estimation of their relative contribution to CV disease, and the development of risk equations to predict CV mortality[6]. These risk equations can be used to identify people who should be prescribed preventive treatments such as statins. Public health campaigns have targeted modifiable risk factors such as smoking, obesity, and lack of exercise.
In Australia, consensus guidelines for the assessment of absolute CV disease risk[7] have been developed. The goal is to reduce the level of absolute risk by managing individual risk factors. The Australian CV risk charts can be used for all adults aged 45 years or over. An exception is made for Aboriginal and Torres Strait Islanders, who should be assessed if they are over 35 years of age. Despite evidence of premature CV morbidity and mortality, there is no recommendation regarding people with chronic mental disorders. The present study was therefore undertaken to investigate CV risk factors in young people with psychosis.

The assessment of CV risk factors in young people with psychosis is complicated by evidence that they differ from the normal population even before they become unwell. Drug naive young people with psychosis are more likely to have impaired glucose tolerance[8] and are more insulin resistant[10] compared with matched controls. Further, type 2 diabetes and schizophrenia share common familial risk factors[11]. Unlike their peers without mental illness, young people with psychotic disorders take antipsychotic medications. The incidence of diabetes and cardiovascular risk (indexed by measures such as body mass index (BMI), total cholesterol, triglycerides and non-fasting glucose) increase after first exposure to any antipsychotic drug[12].

These differences are reflected in studies comparing young people with psychosis and matched general population samples. Our previous work, comparing people with psychosis aged 25-64 years with a matched general population control group, found that even at age 25 years, people with psychosis had a significantly higher mean BMI, waist circumference, triglycerides, diastolic blood pressure and significantly lower HDL-cholesterol than controls [13]. This study did not include people aged less than 25 years as population control data was not available.

In addition, young people with psychosis have much higher rates of tobacco and alcohol use than other young people[14, 15].The reasons for the higher prevalence of use of these substances is unknown; as with diabetes, it is possible that there are common familiar risk factors. These behaviours are associated with adverse effects on physical health and have been identified as risk factors for CV disease.

This study assessed CV risk factors in young people with psychosis. Risk factor equations developed for the general population have not been adapted for young people. The Joint British Societies (JBS3) Board note that current risk estimation is very dependent on age and gender, so young people and women may not be considered for preventive measures, despite high levels of modifiable CV risk factors. There is a move to estimation of lifetime risk, and the JBS3 consensus recommendations for prevention of CV disease (2014) include a lifetime risk calculator. However, the correlational structure among risk factors may be different in people with psychosis, compared with people in the community[16].

We therefore undertook a count of CV risk factors in young men and women with psychosis. This is a simple, easily reproduced method for drawing together information about multiple risk factors in an individual person. A count of CV risk factors may provide useful information about the absolute number and relative prevalence of risk factors. This method does not allow for weighting of the various factors, but does provide a basic structure for longitudinal cohort studies that might then provide this information.

A similar method of counting risk factors was used by Lloyd-Jones et al (2006), analysing the Framingham Heart Study data. They found that the absence of established risk factors (smoking, obesity, hypertension, diabetes, and hypercholesterolemia) at the age of 50 years was associated with very low lifetime risk of CV disease and longer survival. The presence of one risk factor was associated with a reduction in median survival, and those with two risk factors had an even greater reduction in median survival.

We utilised World Health Organisation (WHO) information about the leading global risks for mortality and burden of disease (measured as Disability-Adjusted Life Years or DALYs)[17]. The eight WHO risk factors for high income countries are listed in Table 1. The population attributable fraction of disability and mortality related to each risk factor has been calculated by determining the proportional reduction in population disease or mortality that would occur if this risk factor was reduced to an ideal level. For example, if no one smoked tobacco in high income countries, the death rate would fall by 17.9% and the level of disability in these populations would be reduced by 10.7%.

There is evidence from numerous studies that each of the eight risk factors are more common in people with psychotic disorders than in the general population[18-22]. In a review of six of the WHO risk factors (hypertension, raised glucose, smoking, physical inactivity, overweight/obesity, and elevated cholesterol), Wildgust and Beary (2010) demonstrated that each of these factors are more prevalent in people with schizophrenia than in the general population.

There are some potentially important gender differences. The prevalence of FEP is higher in men, and men tend to be younger at the time of first contact with mental health services[24, 25]. Men are also more likely to smoke tobacco[26] and use alcohol[27]. For these reasons, this current study evaluated risk factors for each gender separately, as well as for the total sample.

No previous studies have applied the WHO-defined risk factor framework in young people with psychosis. The method used in this study, counting up the risk factors to provide a total number for each person, is a novel approach to quantifying CV risks. Systematically drawing together all of the risk factors using this framework provides an integrated, easily understood picture of the total aggregate risk of death and disability, attributable to these specific well-validated factors, faced by a cohort of young people with psychosis. This method does not provide a weighting for the various factors, or tell us the long term implications of having

three rather than two risk factors, but it does introduce a method that may be used in further studies to address these questions, and perhaps ultimately build an informative algorithm. This study analysed data from young people drawn from a large, representative sample of people living with psychosis, to investigate the total number of risk factors present in each individual participant, and prevalence of each of the risk factors in these young people.

Method

This study draws on data from the 2010 second Australian national survey of people living with psychotic illness (Survey of High Impact Psychosis, SHIP). A total of 1825 people aged 18-64 years were interviewed. The survey methods have been described in detail elsewhere[28, 29]. In brief, this study was two-phase sampling design. In phase 1, people in contact with public mental health services and non-government organisations in the previous 12 months were screened for psychosis, resulting in 7955 people screening positive. Those who screened positive were randomly selected during phase 2 to take part in an interview and assessment. Of the 1825 subjects who completed the interview, 1286 provided fasting blood samples. Participants fasted overnight (minimum of 8 hours) then provided venous blood samples for measurement of plasma glucose and total cholesterol concentrations in accredited pathology laboratories. Data was collected regarding participants' gender, age, education, employment, ICD-10 diagnosis and age of onset of psychosis. Diagnoses based on the International Classification of Diseases 10th Revision (ICD-10)[30] were ascertained using the Diagnostic Interview for Psychosis (DIP)[31]. The study was approved by institutional human research ethics committees at each of the study sites. Written informed consent was provided by all participants.

We report here on those 132 people aged 18-24 years who participated in the SHIP interview and provided fasting blood samples. Demographic data included participants' gender, age, education, employment status, and age of onset of psychosis/major affective illness.

WHO Risk Factors: The presence of each of the eight risk factors was determined by applying the WHO criteria[32] to the SHIP data. Tobacco use was defined as smoking tobacco daily in the previous 4 weeks. Blood pressure (BP) was measured by trained research staff while the participant was seated. The WHO criterion for hypertension was systolic BP $\geq$140 mm. Participants were weighed in loose clothing, without shoes, using electronic scales measuring up to 200kg. Overweight and obesity was defined as a body mass index (BMI) $\geq$ 25. Physical inactivity was assessed using the International Physical Activity Questionnaire (IPAQ) short form[33]. Achieving less than 2.5 hours per week of moderate exercise, or less than 1 hour per week of vigorous exercise, was defined as being physically inactive. The WHO (2009) definition of physical inactivity also included people who engaged in less than 600 MET (Metabolic Equivalent of Task) minutes per week of any physical exercise. MET provides a measure of the relative intensity of a physical activity.

High blood glucose was defined as a fasting blood glucose of $\geq$5.6 mmol/l. High cholesterol was defined as a fasting total cholesterol $\geq$6 mmol/l. Whilst the WHO (2009) defines low fruit and vegetable intake as less than 5 serves of fruit and vegetables daily, in our data low fruit and vegetable intake was defined as consuming fewer than 4 daily servings of fruit (1 serve = 1 medium piece or 2 small pieces of fruit or 1 cup of diced pieces = 150 grams) and vegetables (1 serve = 1/2 cup cooked vegetables or 1 cup of salad vegetables = 75 grams). Our data therefore tends to underestimate low fruit and vegetable intake. Alcohol abuse was

defined as an average daily consumption of 4 or more standard drinks per day, four or more times per week.

Statistical analysis: Data were analysed using SPSS version 21; IMB Corp., 2012. Individual risk factor variables were coded as binary (0 = not present; 1 = present). Risk factors for each participant were summed to obtain a single variable, representing the total number of risk factors for that person. Descriptive statistics were used to summarise participant characteristics. The sample was stratified by gender, and the number of risk factors in each gender was compared. These comparisons were made using X^2 tests and p values < 0.05 were taken as significant.

Results

Fasting blood samples were provided by 64.7% (n= 132/204) of SHIP participants aged 18-24 years. There were no differences in age, gender or education between people who supplied a fasting blood sample and those who did not. Descriptive data for the 132 participants in this study is summarised in Table 2.

The total number of risk factors present, by gender, is shown in Table 3. There was no significant difference in the mean number of risk factors present between men and women. The prevalence of each risk factor is shown in Table 4. The most common risk factors were low fruit and vegetable intake, smoking, overweight/obesity and physical inactivity. Young men had an average of 2.9 (SD 1.2) risk factors and young women had an average of 2.4 (SD 1.2) risk factors; this difference was not significant. There were no significant gender differences in the prevalence of each individual risk factor.

Table 1. Percentage of DALYs[*] and Deaths for each WHO risk factor in high income countries.

Risk factor	DALYs (%)	Deaths (%)
Tobacco use	10.7%	17.9%
High blood pressure	6.1%	16.8%
Overweight and obesity	6.5%	8.4%
Physical inactivity	4.1%	7.7%
High blood glucose	4.9%	7.0%
High cholesterol	3.4%	5.8%
Low fruit and vegetable intake	1.3%	2.5%
Alcohol use	6.7%	1.6%

*DALY = disability- adjusted life year. One DALY = one lost year of 'healthy' life.[32]

Table 2. Characteristics of people with psychosis aged 18-24 years who provided fasting blood samples.

| | 18- 24 years (n =132) |
	% (n)[†] or M(SD)
Sex	
Male	65.9%
Female	34.1%
Age (years)	
Mean (SD)	21.51 (1.77)
Education	
Left school with no qualifications	38.2%
Secondary school qualification	19.8%
Vocational, university or other qualification	42.0%
Currently unemployed	75.8%
ICD-10 Diagnoses	
Schizophrenia/schizo-affective disorder	69.7%
Bipolar disorder with psychotic features	9.1%
Psychotic depression	5.3%
Other psychosis	15.9%
Mean age of illness onset (years)	17.34 (2.52)

[†] Where complete data were not ascertained, the number of responses available is also reported.

Table 3. Total number of WHO CVD risk factors (RF's) in men and women with psychosis aged 18-24 years.

Total number of WHO risk factors	men 18-24 years % (n)	women 18-24 years % (n)	Total % (n)	χ^2 value	p value
0	1.2% (n= 1)	7.7% (n= 3)	3.3% (n= 4)	6.65,	0.355
1	10.8% (n= 9)	15.4% (n= 6)	12.3% (n= 15)		
2	28.9% (n= 24)	30.8% (n= 12)	29.5% (n= 36)		
3	22.9% (n= 19)	25.6% (n= 10)	23.8% (n= 29)		
4	26.5% (n= 22)	17.9% (n= 7)	23.8% (n= 29)		
5	8.4% (n= 7)	2.6% (n= 1)	6.6% (n= 8)		
6	1.2% (n=1)	0% (n=0)	0.8% (n= 1)		
7 or 8	0% (n= 0)	0% (n= 0)	0% (n= 0)		

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Table 4. Prevalence of individual WHO risk factors in men and women with psychosis aged 18-24 years.

Individual WHO Risk factors	Men 18-24 years % (n)	Women 18-24 years % (n)	Total 18-24 years	χ^2 value	p value
Tobacco use	72.1% (n= 62/86)	59.1% (n= 26/44)	67.7% (n= 88/130)	1.70	0.193
High blood pressure (systolic BP ≥140 mmHg)	8.0% (n= 7/87)	6.8% (n= 3/44)	7.6% (n= 10/131)	0.00	1.000
Overweight/obese (BMI ≥ 25)	57.5% (n= 50/87)	50.0% (n= 21/42)	55.0% (n= 71/129)	0.37	0.542
Physical inactivity	41.2% (n= 35/85)	37.2% (n= 16/43)	39.8% (n= 51/128)	0.06	0.809
High blood glucose or diabetes (≥ 5.6 mmol/l)	16.1% (n= 14/87)	6.7% (n= 3/45)	12.9% (n= 17/132)	1.58	0.208
High total cholesterol (≥ 6 mmol/l)	12.6% (n= 11/87)	6.7% (n= 3/45)	10.6% (n= 14/132)	0.58	0.448
Low fruit and vegetable intake (less than 4 daily servings)	79.1% (n= 68/86)	75.6% (n= 34/45)	77.9% (n =102/131)	0.06	0.812
Alcohol use (≥ 4 drinks per day, 4 or more times a week)	8.2% (n= 7/85)	4.4% (n= 2/45)	6.9% (n= 9/130)	0.20	0.655

Discussion

Ideally, young people should not have any of the WHO-defined risk factors for cardiovascular disease. Apart from rare genetic conditions (such as familial hypercholesterolemia), all of the eight risk factors investigated in this study are potentially preventable by lifestyle measures. The young people in this study already had, on average, 2-3 risk factors. Thirty men and eight women had four or more risk factors.

Obesity and smoking are responsible for 17.9% and 8.4% of mortality in high income countries respectively, and were each present in more than half of our study sample. Poor diet and lack of exercise were also common, and would be expected to contribute to a gradual increase in obesity over time. Other risk factors such as hypertension, hypercholesterolemia and diabetes can be expected to develop later, in the context of chronic obesity, poor diet and physical inactivity.

It is informative to be able to compare our results with general population data. We are not aware of any studies of Australian young people incorporating all of these WHO risk factors, but there is information about some individual measures. Over half of people in our study were overweight or obese, which is more than three times the prevalence of overweight/obesity in Australians of the same age (15.1%)[34]. In the general Australian population, 18.3% of men and 14.8% of women aged 18-24 years smoke tobacco daily. Rates of smoking amongst our study population are very high with more than two thirds (67.7%) of our sample being current smokers. Hypertension was slightly more prevalent in our psychosis sample, with 8% of men and 6.8% of women having elevated blood pressure, compared with 6.8% of men and 5.2% of women aged 18-24 years in the general Australian population (ABS, 2012).

Australia has a well-developed social welfare system to support people with mental illness, and the SHIP sample was drawn from people in contact with mental health services. In some catchments, early psychosis services were also available. Despite these supports, their physical health status was poor. It is therefore essential that services for young people with psychosis place a high priority on the management of their physical health. All of the WHO risk factors are potentially modifiable through low cost interventions such as diet, exercise, and cessation of smoking and alcohol abuse. Curtis et al (2015) evaluated a lifestyle and life skills intervention for young people (14-25 years) with early psychosis, who were starting treatment with antipsychotic medication. Only 13% of the intervention group experienced significant weight gain, compared to 75% of the standard care group.

The very high rates of smoking in young people with psychosis has raised the possibility that tobacco might contribute to the aetiology of psychosis[37], which would mean that it is even more imperative that young people are encouraged and assisted to stop smoking. There is little research into smoking cessation interventions for young people with psychosis, but studies in adults with chronic mental illness[38] and a systematic review of smoking cessation interventions in people with schizophrenia[39] have both shown encouraging results. Similarly, Baker et al (2015) reported some improvements with an intervention targeting both smoking and cardiovascular risk factors in people with psychotic disorders.

However, research into physical health interventions predominantly consists of trials of modest duration with small numbers of participants. Gates et al (2015) note that while weight loss and attenuation of weight gain are possible, these positive benefits might not persist beyond the end of the intervention. For example, a three month behavioural intervention

combining information on nutrition and exercise in a randomized controlled trial in patients with first-episode psychosis attenuated the weight gain caused by antipsychotic medication[42] but the differences were no longer significant at 12 month follow up[43]. Gates et al (2015) highlight the need for investigation into the aetiological factors related to poor physical health and for theory-driven interventions that target these aetiological factors. Further, larger and more sustainable results are likely to come from improved, integrated medical management of patients, with interventions like smoking cessation programs offered to appropriate individuals at times that they are most likely to benefit from them. There is a risk that short-term programs with goals that are difficult to achieve may result in further experiences of failure and demoralisation.

This study provides information for planning intervention programs; clearly it would be sensible to target the risk factors that are most common, and associated with the most severe disability and risk of mortality. A focus on prevalence is simplistic, however, because prevalence does not equate to the impact of the risk factor or the achievable risk reduction associated with current intervention paradigms. Determining these requires longitudinal multivariate risk and outcome data in large samples of people with psychosis. Even so, as shown by Lloyd-Jones et al (2006), simply noting the presence and number of risk factors can predict median survival.

A clear methodological limitation in this study is the relatively small sample size after gender and age stratification. Furthermore, our measure underestimated low fruit and vegetable intake; even so, 77.9% of participants had inadequate intake. There is also a lack of control data for people in the general population aged 18-24 years. This study did not record family history of CVD, CKD and cancer. Comprehensive assessment of multiple risk factors and the use of the epidemiological data informing risk of disability and death is a strength of the study. Nevertheless, the findings are stark and underline the importance of physical interventions being an integral part of comprehensive care for people with an early psychosis.

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Overall percentage (%)	80%		
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ii.   permission is granted for the candidate in include the publication in the thesis; and

iii.   the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Objective

This study explored the prevalence of multiple risk factors for morbidity and mortality in people with psychosis aged 18-64 years.

Method

The study included 1156 people aged 18-64 years, diagnosed with psychosis. The 2009 World Health Organisation (WHO) Global Health Risks Report was used as a framework to determine which eight risk factors for cardiovascular disease (CVD) were present in men and women. A count of the total number of risks was determined. Change in the number and type of risk factors with age and gender was investigated by comparing the 18-34 and 35-64 year age groups in men and women.

Results

Older men had more risk factors than younger men (3.73; SD 1.35 vs. 3.26; SD 1.28) (p <0.0001); older women had more risk factors than younger women (3.38; SD 1.30 vs. 2.81; 1.20) (p <0.0001). Overweight/obesity, hypertension, high blood glucose/diabetes and high cholesterol were significantly more prevalent in older men and women compared with younger men and women. Older men were more likely to be physically inactive than younger men (p <0.0001); younger men were more likely to use tobacco than older men (p <0.01).

Conclusion

People with psychosis have a high prevalence of CVD risks. There were age and gender differences in the pattern of these risks. Apart from smoking, the distribution of biomedical risks increased with age. These risks were more common in men, reflecting the necessity of close monitoring at the clinical level. The most common risk factors should be able to be impacted by lifestyle interventions.

Keywords: Psychosis, Cardiovascular disease, Risk factors, Morbidity, Mortality

1. Introduction

The poorer health outcomes and premature mortality of people with psychotic disorders (including schizophrenia) compared with the general population, are well recognised (Laursen et al., 2013, Laursen et al., 2014). Cardiovascular disease (CVD) is the leading cause of premature death in people with schizophrenia (Ringen et al., 2014). The average risk for developing cardiovascular (CV) pathology is much higher in men and women with schizophrenia (9.4% and 6.3%) compared to men and women in the general population (7.4% and 4.2%), (Goff et al., 2005). A more recent study revealed that excess deaths due to CVD were more common in women than men with schizophrenia (Lawrence et al., 2013), suggesting that the presence of risk factors may not explain all gender differences in CVD outcomes. It is important to be able to identify, and quantify, the risk of CV disease faced by each individual patient with schizophrenia and other psychotic disorders. Risk calculators have been developed for the general population, based on large longitudinal cohort studies (Pencina et al., 2009). However, the differences in CV risk between people with psychotic illnesses and the general population (attributed to the effects of some antipsychotic medications) would be expected to impact on the accuracy of risk calculators.

There has been considerable research into the prevalence of physical health problems in people with psychotic disorders. Metabolic syndrome is found in about one third of people with schizophrenia and related disorders, compared to matched general population controls; equating to a relative risk of 1.58 (Vancampfort et al., 2015). There are differences in the prevalence of metabolic syndrome between people taking different antipsychotic medications (Vancampfort et al., 2015). Weight gain can occur early in the course of treatment (Foley and Morley, 2011).

The World Health Organisation (WHO) identified eight risk factors that contribute to cardiovascular morbidity and mortality in high income countries (pg 28 WHO., 2009). These risk factors are smoking, hypertension, high body mass index (BMI), physical inactivity, high blood glucose, high cholesterol, inadequate consumption of fruit and vegetables and excessive alcohol intake (Table 1). These eight CV risk factors together are estimated to account for 61% of disease burden and 61% of deaths in these countries (WHO, 2009). Urban outdoor air pollution and occupational risks were excluded from this study due to the lack of data that was available for these variables.

There is evidence that each of the eight CV risk factors are more common in people with psychosis than in the general population. Odd ratios measuring the association of these risk factors in people with schizophrenia compared with the general population have previously been reported: current smoking (OR= 5) (de Leon and Diaz, 2005); hypertension and diabetes (OR=2-3) (Stubbs et al., 2015) (De Hert et al., 2009); obesity (OR= 1.5-2) and harmful alcohol use (OR= 2) (McCreadie, 2002). Twenty six percent of the psychosis population are physically inactive compared with 18% of controls (Daumit et al., 2005) and they have a more than doubled risk of low HDL cholesterol. (Vancampfort et al., 2013). Most people with psychosis fail to meet dietary requirements for fruit and vegetable intake (74%) (Hahn et al., 2014). A review by Wildgust and Beary (2010) revealed that six of the WHO risk factors (smoking, hypertension, overweight/obesity, physical inactivity, raised glucose and elevated cholesterol), were more prevalent in people with schizophrenia than in the general population.

There are no studies investigating the total number of WHO-defined CV risk factors in people with psychosis. In this study, we counted CV risk factors in a representative national sample of men and women with psychosis. This is a simple, easily reproduced method for drawing together information about multiple risk factors in an individual person. A count of CV risk factors provides information about the absolute number and relative prevalence of risk factors that can be useful in assessing the overall change in CV risk profile after the introduction of intervention programs.

This method does not allow for weighting of the various factors, but does provide a basic structure for longitudinal cohort studies that might then provide this information. A similar method of counting risk factors was used by Lloyd-Jones et al (2006), analysing the Framingham Heart Study data. They found that the absence of established risk factors (smoking, obesity, hypertension, diabetes, and hypercholesterolemia) at the age of 50 years was associated with very low lifetime risk of CV disease and longer survival. The presence of one risk factor was associated with a reduction in median survival, and those with two risk factors had an even greater reduction in median survival.

This study used a large representative sample of adults (aged 18-64 years) who have psychosis, to explore the prevalence of the eight CVD risk factors that are outlined by WHO.

2. Methods

2.1. Study population

This study uses data from the 2010 second Australian survey of people living with a psychotic illness. The sample comprised of 1825 people aged 18-64 years who were interviewed by trained research staff. Morgan et al. (2012., 2014) provides more detail about the methods used in this study. A two-phase sampling design was used. In phase 1, people in contact with public mental health services and non-government organisations in the prior 12 months were screened for psychosis. This resulted in 7955 people screening positive. People who screened positive were randomly chosen during phase 2 of the study to participate in interview and assessment, and 1825 subjects completed the interview. Of these, 1286 people provided fasting blood samples, where participants fasted overnight (minimum of 8 hours) then gave venous blood samples for measurement of plasma glucose and total cholesterol concentrations in accredited pathology laboratories.

There were 1156 (94.8%) people diagnosed with affective or non-affective psychosis, who provided a fasting blood sample. There were no significant differences for age, marital status, employment, diagnoses and education between those who gave blood samples (n=1156) and those who did not (n= 64). Though, there was a significant difference between fasting blood samples provided by men (n= 711; 61.6%) and women (n= 444; 38.4%). Institutional human research ethics committees approved the study at each of the seven study sites across Australia and written informed consent was provided by all participants.

2.2. Data collection and risk factor assessment

The Diagnostic Interview for Psychosis (DIP) (Castle et al., 2006) was used to make diagnoses based on the International Classification of Diseases 10th Revision (ICD-10) (World Health Organization, 1992). Demographic data included gender, mean age, diagnosis, education status, employment status and mean age of illness onset.

The WHO (2009) have provided operational definitions of the risk factors used in this study. Tobacco use was defined as a person smoking tobacco during the last four weeks. Blood pressure (BP) was measured by trained research staff while the person was seated for at least 5-10 minutes. The cut off criterion for hypertension was a systolic BP > 140 mm Hg. A body mass index (BMI) ≥25 indicated the presence of overweight or obesity. Participants were weighed in loose clothing without shoes, using electronic scales measuring up to 200kg.

Physical inactivity was assessed using the International Physical Activity Questionnaire (IPAQ) short form (Craig et al., 2003). People reporting less than 2.5 hours per week of moderate exercise, or less than 1 hour per week of vigorous exercise were classified as physically inactive. People achieving less than 600 MET (Metabolic Equivalent of Task) minutes per week of any physical exercise were also classified as physically inactive

High blood glucose included a fasting blood glucose level ≥5.6 mmol/l. High total cholesterol was defined as a fasting total cholesterol ≥ 6 mmol/l. Low intake of fruit and vegetables was defined as consuming less than 4 daily servings of fruit (150 grams per serve) or vegetables (75 grams per serve). Risky alcohol use was defined as consuming 4 or more standard drinks per day, four or more times per week.

2.3. Data analysis

Data were analysed using SPSS version 21; IMB Corp., 2012. Descriptive statistics were used to summarise participants' demographic data. Individual risk factors were coded as binary (0 = absent; 1 = present). Individual risk factors were summed to obtain a total count of risk factors for each participant. The sample was stratified by age group (18 to 34 years and 35 to 64 years) for gender; individual risk factors and total number of risk factors was compared by age group and by gender. Group differences were assessed using a χ^2 test, with a $p < 0.05$ indicating significance, to determine the effect of age within gender on the number and type of risk factors present.

3. Results

Table 1 shows the percentage of DALY's and deaths for each WHO risk factor in high income countries. For example, in the general population in a high income country, tobacco use accounts for 17.9% of deaths, and the loss of 10.7% of years of healthy life.

A summary of participants' characteristics is provided in Table 2. The prevalence of the individual WHO-defined risk factors presented by age, for men and women, is shown in Table 3. The distribution of risk factors changed with age. Older men and women (aged 35-64 years) were significantly more likely to have hypertension, be overweight or obese, have high blood glucose or diabetes, and have high total cholesterol, compared with their younger counterparts (18-34 years). Older men were more likely to be physically inactive compared with younger men, but this difference was not found among women. Younger men were more likely to use tobacco compared with older men and again this difference was not observed in women. Overall, men were significantly more likely to use tobacco and alcohol, have a low consumption of fruit and vegetables and have systolic hypertension compared to women.

The total number of risk factors present, by age and gender, is shown in Figure 1. There was a significant difference in the total number, and mean number of risk factors between

younger men and older men and between younger women and older women. Men aged 18-34 years had an average 3.26 (SD 1.28) risk factors and men aged 35-64 years had an average 3.73 (SD 1.35) risk factors. Women aged 18-34 years had an average 2.81 (SD 1.20) risk factors and women aged 35-64 years had an average 3.38 (SD 1.30) risk factors.

Table 1. Percentage of DALYs[*] and Deaths for each WHO risk factor in high income countries.

Risk factor	DALYs (%)	Deaths (%)
Tobacco use	10.7%	17.9%
High blood pressure	6.1%	16.8%
Overweight and obesity	6.5%	8.4%
Physical inactivity	4.1%	7.7%
High blood glucose	4.9%	7.0%
High cholesterol	3.4%	5.8%
Low fruit and vegetable intake	1.3%	2.5%
Alcohol use	6.7%	1.6%

*DALY = disability- adjusted life year. One DALY = one lost year of 'healthy' life. (WHO, 2009).

Table 2. Characteristics of people with psychosis aged 18-64 years (n = 1156).

	% (*n*) or M(SD)
Sex	
Male	61.6% (712)
Female	38.4% (444)
Age (years)	
18-34	42.3% (489)
35-64	57.7% (667)
Mean age (years)	
Mean (SD)	38.39 (10.97)
Marital Status	
Single, never married	60.4% (698)
Currently married or Defacto	17.7% (205)
Currently separated, divorced or widowed	21.9% (253)
Education	
Left school with no qualifications	34.4% (396/1150)
Secondary school qualification	16.4% (189/1150)
Vocational university or other qualification	49.1% (565/1150)
Currently unemployed	79.8% (922)
ICD-10 Diagnoses	
Schizophrenia	51.1% (591)
Schizo-affective disorder	18.3% (211)
Bipolar disorder with psychotic features	19.5% (225)
Psychotic depression	5.4% (63)
Delusional disorders and non-organic psychosis	5.7% (66)
Mean age of illness onset (years)	23.68 (8.50)

Table 3. Prevalence of individual WHO-defined risk factors in men and women with psychosis aged 18-34 years and 35-64 years.

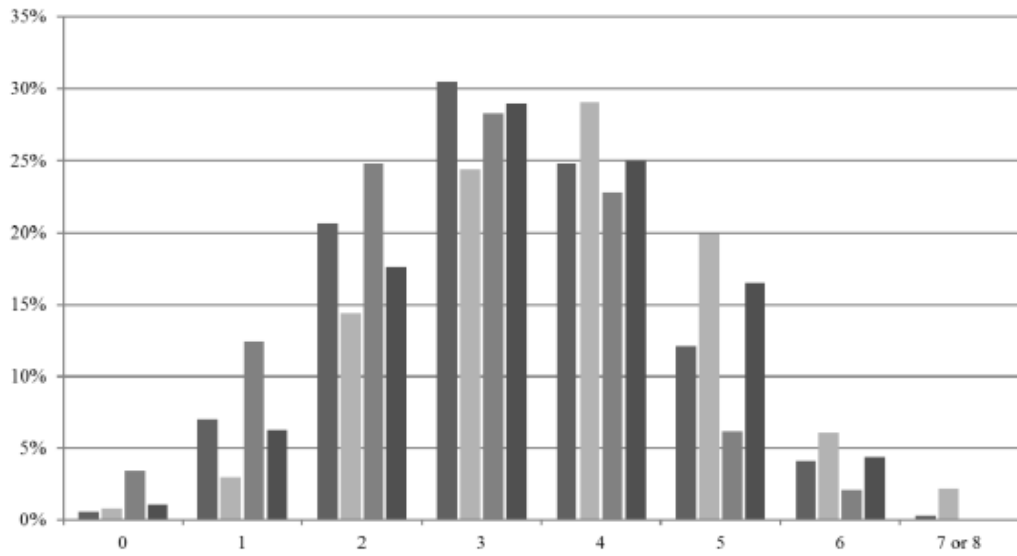| Total number of WHO risk factors	Men 18-34 years	Men 35-64 years	χ^2 value	p value	Women 18-34 years	Women 35-64 years	χ^2 value	p value
	% (*n*)	% (*n*)			% (*n*)	% (*n*)		
Tobacco use	76.2%(247/324)	65.4% (250/382)	9.28	<0.01	58.9% (93/158)	56.5% (160/283)	0.14	0.709
High blood pressure (systolic BP ≥140 mmHg)	9.2% (30/326)	23.7% (89/376)	24.94	<0.0001	1.9% (3/154)	14.4% (40/277)	24.94	< 0.0001
Overweight/obese (BMI ≥25)	71.3% (233/327)	82.5% (311/377)	11.96	<0.01	72.7% (112/154)	84.2% (234/278)	7.44	<0.01
Physical inactivity	40.7% (133/327)	55.3% (209/378)	14.42	<0.0001	44.2% (68/154)	52.3% (148/283)	2.33	0.127
High blood glucose or diabetes (≥5.6 mmol/l)	22.2% (73/329)	32.8% (125/381)	9.38	<0.01	12.5% (20/160)	28.6% (81/283)	14.19	<0.0001
High total cholesterol (≥ 6 mmol/l)	18.5% (61/329)	26.6% (102/383)	6.11	<0.05	11.9% (19/160)	27.5% (78/284)	13.67	<0.0001
Low fruit and vegetable consumption (< than 4 daily servings)	78.0% (255/327)	76.5% (289/378)	0.15	0.695	72.8% (115/158)	69.0% (196/284)	0.52	0.469
Alcohol use (> 4 drinks per day, 4 or more times a week)	11.1% (36/325)	11.5% (44/382)	0.00	0.948	5.6% (9/160)	4.2% (12/283)	0.18	0.670

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Figure 1. Total number of risk factors present by age and gender.

- Men 18-34 years
- Men 35-64 years
- Women 18-34 years
- Women 35-64 years

4. Discussion

A number of biomedical risk factors, apart from smoking (overweight/obesity, high blood pressure, high blood glucose and high cholesterol) were more prevalent in older than younger men and women with psychosis in this study. Our previous work comparing cardiovascular (CV) risk in people with psychosis and the general population showed that at-risk thresholds for BMI, diastolic blood pressure, LDL-cholesterol, triglycerides and blood glucose, were exceeded at an earlier age in psychosis compared with controls (Foley et al., 2013).

Cardiovascular risks are present at an early age in psychosis and worsen with increasing age (Bresee et al., 2010). Second generation antipsychotic drugs are known to induce adverse metabolic outcomes (obesity, hyperglycaemia, dyslipidaemia and hypertension) (De Hert et al., 2012), thus, individuals with psychosis are likely to experience an early onset of cardiovascular disease. A positive relationship between age and diabetes, hypertension, dyslipidaemia and CV disease has previously been found in people with schizophrenia compared with the general population and appear to highlight a 'metabolic ageing effect' that is more pronounced in people with psychosis than people in the general community (Bresee et al., 2010).

Approximately three quarters of young men in this study used tobacco and this was significantly higher than in older men. This was unexpected, as in the normal population, smoking generally increases with age and begins to decline from 55 years of age (Australian Institute of Health and Welfare, 2015). Despite the prevalence of smoking remaining high across both age groups, perhaps older men in our study are receiving smoking advice from health professionals as they are presenting with a higher number of CV risks. Older men were more likely to be physically inactive compared with their younger counterparts. The health benefits of exercise have been well documented (Li and Siegrist, 2012). Given that older men and women in this study had more CV risk factors, exercise should strongly be promoted to improve their CV health. Physical activity supports weight loss and this could help with the management of diabetes, hypertension and high cholesterol (Williams and Thompson, 2013) that is often affected through antipsychotic therapy.

A higher prevalence of CV risk factors was found in men compared with women in our study, coinciding with earlier findings by Goff et al (2005). Tobacco use, alcohol use, low consumption of fruit and vegetables and systolic hypertension were all higher in men than women. However, women with schizophrenia have more excess deaths due to CVD compared with men (Lawrence et al., 2013), suggesting that there may be other factors contributing to this excess mortality among women.

Smoking rates in men and women in this present study were well above national levels compared to men and women in the general population (70.4% versus 20.4%) and (57.4% versus 16.3%) respectively (Australian Bureau of Statistics, 2013). Excessive alcohol consumption was significantly more common in men than women. Even drinking more than two standard drinks on any day can increase the lifetime risk of harm from alcohol-related disease or injury (Australian Institute of Health and Welfare, 2015).

Approximately three quarters of our participants failed to meet guidelines for daily fruit and vegetable intake. Simonelli –Munoz and colleagues (2012) reported that in a sample of people living with schizophrenia in Spain, 91% of consumed less than four daily servings of fruit or vegetables (Simonelli-Munoz et al., 2012). This suggests that Australians with

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psychosis may be doing better in terms of nutritional intake compared with international studies. General population comparisons for fruit and vegetable intake were difficult to obtain for this current study.

Research examining the association between fruit and vegetable consumption and all-cause mortality using a large population based cohort (n= 71, 706) showed that people who never consumed fruit or vegetables had a 53% higher mortality rate than people who consumed five daily servings of fruit or vegetables (Bellavia et al., 2013). It appears that people with psychosis are at risk of poor CV health outcomes associated with not eating an adequate diet.

Systolic hypertension was more common in men than women in this study. Raised blood pressure changes the structure of the arteries, ultimately increasing the risks of stroke, heart disease and kidney failure (World Health Organisation, 2009). High total cholesterol, and high blood glucose or diabetes, were each found in approximately one quarter of our participants. These risks are often undiagnosed in the general population (Gupta and Gupta, 2002, Cowie et al., 2009) but people with chronic mental illness are at greater risk of receiving poor medical care overall, therefore, they are less likely to be treated for these conditions (Nasrallah et al., 2006, Hardy et al., 2013).

More than three quarters of our sample were overweight or obese. Our previous work exploring CV risk in psychosis compared with the general population, showed that BMI was greater, compared with the normal population comparator sample, from ages 25-64 years (Foley et al., 2013). Obesity can be attenuated through exercise and a healthy diet, but addressing obesity in people with psychosis is complex. Targeting diet and exercise can also be effective in managing Type 2 diabetes and high blood pressure; however, factors such as cognitive impairment, limited resources, amotivation and obesity pose significant challenges in people with psychosis, suggesting that such interventions need to be tailored around the individual needs of the patients. Gates et al. (2015) report that while weight loss is achievable through non-pharmacological interventions, the positive benefits, to date, have not been sustained post-intervention.

Of the 8 WHO-defined CV risk factors in this study, older men and women had a higher mean number of risk factors than their younger counterparts, suggesting that early intervention may prevent the accumulation of risk factors with age. An increase in the presence of risk factors can increase the lifetime risk of CVD. Having more than two major risk factors can increase the lifetime risk of CVD risk by more than 10% compared to having one major risk factor (Berry et al., 2012). To date, there is no available population level data using the WHO-defined risk factors, to compare the presence of multiple risk factors. There is data showing that Australians have on average 2-3 risk factors out of a total of 9 risk factors (smoking, risky alcohol consumption, physical inactivity, high blood pressure, high total cholesterol, diabetes, obesity, low fruit consumption and low vegetable consumption) (Australian Institute of Health and Welfare, 2005) but this was self-reported data without fasting blood tests.

4.1. Limitations

Several methodological limitations are present in this study. The study was a cross-sectional design and while it formed part of a large national cohort of 1825 participants, we only included people who provided fasting blood samples. The WHO measure poor intake of fruit and vegetables as consuming less than 5 daily servings; however, we were unable to match this measure in our study. Therefore, the present study underestimates the proportion of

people who have an inadequate diet. Population data regarding the presence of the multiple 8 WHO-defined risk factors is lacking; we were unable to make comparisons with our sample.

4.2. Conclusions

The method of utilising a risk factor count in this study is a novel approach to obtaining an overall risk profile among individuals or large groups of people with psychosis. This could inform future studies of the prediction of short term or long term risk of CVD. This method can help determine whether there is an overall change in the level of CV risk factors after intervention programs are undertaken. Importantly, risk factor counting can be used as a means of employing cost-effective interventions in addressing primary prevention. This study demonstrated that the CV risk profile in men and women got worse with age. Men have a higher prevalence of these risks than women. Intervention services, including early interventions, designed to target these risks is paramount to prevent CV illness.

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CHAPTER 8: General Conclusion

Overview of Thesis Aims

The general aim of the current thesis was to investigate the presence of risk factors for cardiovascular disease (CVD) among people with psychosis, using the same risk factors outlined by the World Health Organisation (WHO) as they represent the greatest contribution to morbidity and mortality.

The thesis was divided into two sections, each one covering a different research aim. The first section, titled "Individual risk factors for Cardiovascular Disease," was led by the following research questions:

- Are the characteristics of people who fail to meet dietary recommendations different to those who do meet dietary recommendations, and if so, what factors specifically predict poor dietary adherence? (Paper 1)

- What is the quantity of nutrients consumed by people with psychosis and is this in excess, or below to what is the recommended dietary intake? Is nutrient intake in people with psychosis different to the nutrient intake among people in the general population? (Paper 2).

- What are the blood pressures in people with psychosis? Are factors that are related to pulse pressure (PP) and mean arterial pressure (MAP) in the general population, the same among people with psychosis? (Paper 3).

The second section of the thesis titled "Total Number of Risk Factors Present" was guided by the following research questions:

- Is the total number of risk factors different in young men and young women with psychosis? (Paper 4).

- Is the total number of risk factors in younger men different to the total number of risk factors in older men? Is the total number of risk factors in younger women different to the total number of risk factors in older women? (Paper 5).

Summary of Research Findings

Section A: Individual Risk Factors for Cardiovascular Disease

Paper 1

This paper was the first study to investigate the national prevalence of dietary compliance in a large sample of people with psychosis. In addition, paper 1 introduced several variables for analysis relating to demographics, physical health, drug use, physical activity, symptom severity and financial hardship to determine whether these factors, were indeed, associated with a poor diet. The study was based on participants who provided fasting blood samples, in order to obtain accurate data on a range of metabolic indices. Importantly, around three quarters of participants failed to meet dietary recommendations for fruit and vegetable intake. While this was significantly associated with a lower body mass index (BMI), decreased exercise levels, substance use, worse psychiatric symptoms, poorer food choices and financial difficulty, current smoking appeared to be the strongest driver of dietary non-compliance, over and above methamphetamine use and cannabis use. In particular, people who were younger age and male were at risk of poorer fruit and vegetable intake. Given the value of these findings, the real strength of this paper was highlighting the negative impact that smoking has on dietary intake and the possible consequence of fruit and vegetable consumption being increased, if smoking behaviour was reduced.

This set of findings clarified the national prevalence of dietary recommended intake using well-validated dietary criteria that is known to have an impact on disease and mortality. This study showed that the relationship between poor diet, male gender and younger age reported in previous literature in the general population, also extends to people with a severe mental illness. In the context of national research, paper 1 demonstrated that, in Australia, fruit and vegetable consumption was higher, in comparison to Europe. Importantly, paper 1 provided further insight into nutrient intake in people with psychosis. As expected, people with psychosis had a lower consumption of these foods compared to the wider community.

Paper 2

This paper extended the findings of paper 1 to a smaller subset of people with psychosis residing in South Australia. Like paper 1, paper 2 also explored dietary consumption, but in this paper, dietary consumption was measured according to the quantity of macro and micro nutrient intake and whether this level of intake was above or below the recommended thresholds. The quantity of specific nutrients consumed was also compared with the

Australian population. It was demonstrated that most of the sample did not meet the recommended dietary intakes for fruit, vegetables, fibre, fish, magnesium, or folate. Regarding fruit and vegetable consumption, these findings offer support for paper 1 in reaffirming that fruit and vegetable consumption is insufficient and unlikely to meet recommendations. The findings among people with psychosis were different from people in the general population. A population comparison revealed a higher intake of vitamins and minerals among women with psychosis compared with women in the normal population. Adults with psychosis consumed a higher intake of daily total fat, saturated fat and sodium opposed to adults in the normal population. However, fibre intake and vitamin E intake was lower in people with psychosis than the general population. Overall, paper 2 was an elaborated version of paper 1, in terms of the breakdown of fruit and vegetables into nutrient constituents.

Paper 2 provided clarification on the nutrient intakes in individuals with psychosis, with respect to assessing various macro and micro-nutrient components which provided a broader overview of nutrient consumption. Outcomes of this study confirmed previous findings that people have a poor diet characterised by low intake of fruit, vegetables and fibre but an excess intake of saturated fat and sodium. The findings in this paper revealed the significantly increased consumption of vitamins and minerals (fish, iron, phosphorous, potassium, zinc, niacin equivalents and thiamin) among women with psychosis compared with women in the general population, which adds support to prior findings that suggest women with schizophrenia consume more total calories than women in the general population. Thus, paper 2 was successful in establishing that while people with psychosis consume more vitamins and minerals than the general population, they also have an excess consumption of total fat, saturated fat and sodium that is above the recommended dietary intake that may heighten their risk of cardiovascular disease (CVD).

Paper 3

This paper was another investigation into one of the individual risk factors that contribute to the development of cardiovascular (CV) illness. This paper utilised the same study participants from paper 1 and was the first study to investigate associations of arterial elasticity (pulse pressure) and peripheral resistance (mean arterial pressure) in a large cohort of people. Older men in particular, had a higher PP and MAP compared to women. A higher PP and MAP was associated with unmodifiable risk factors such as male gender, higher age and having a family history of hypertension, which illustrated to be different from the general

population, where these different blood pressure components were associated with modifiable risks.

This paper offered a fresh insight into associations of blood pressure by focussing on PP and MAP, which measure arterial elasticity and peripheral perfusion. This is different form systolic and diastolic blood pressure, which measure the pressure in the arteries when the heart beats or when the heart rests between beats. These set of findings are new as investigations into PP and MAP have not been previously undertaken among a large sample of people with psychosis. This paper offered insight into PP and MAP in participants who are established on antipsychotic medication, relative to people with first episode psychosis (FEP) and healthy controls that were from prior research. Importantly, paper 3 expanded on traditional blood pressure components (SBP and DBP) by identifying factors that impact upon arterial elasticity and peripheral resistance that ultimately increase the risk of CVD.

Paper 3 supported one finding in the normal population relating to obesity and higher MAP. Most of the findings in this paper did not coincide with the normal population; thus, paper 3 demonstrated that people with psychosis and people in the general population may have different risks that elevate PP and MAP.

Taken together, the findings from these three papers have identified various risks that are associated with poor diet and increased blood pressure. Paper 2 was a closer examination of dietary behaviour that provided a general population comparison of nutrient intake. Concurrently, the papers narrowed the gap in the literature regarding the identification of risk factors that are associated with inadequate nutrient intake and increased blood pressure. The papers demonstrated that these risks are related to various factors including substance use, demographics, physical health and genetic history.

Section B: Total Number of Risk Factors Present

Paper 4

The fourth paper of the thesis applied a risk factor count in 132 young people to identify the total number of risk factors for cardiovascular disease (CVD). A risk factor count represents a unique approach for obtaining a broader picture of the total number of risks present, that ultimately impact upon CV related morbidity and mortality. This method of quantifying CV risks was partly adapted from Lloyd-Jones et al (2006), where it was shown that having multiple risk factors was associated with a greater lifetime risk of CVD in comparison to having one risk factor. Thus, the utility in applying a risk factor count was evident; as this

could possibly be extended in future studies through the formulation of an informative algorithm.

Paper 4 demonstrated that young men and women differed according to their total number of risk factors. On average, young men had approximately 3 risk factors, and young women had approximately 2 risk factors. This study also highlighted that certain individual risk factors were more common than others. Many of the behavioural risk factors including smoking, poor diet and physical inactivity existed between 40-78% of the sample, with poor diet and tobacco use being the two leading risk factors present. Over half of the sample was overweight or obese. Biomedical risks relating to high cholesterol, high blood glucose or diabetes and hypertension were present in 8-13% of the sample. Hypertension was the only risk factor that was statistically significant according to gender, as men presented with a higher incidence of hypertension than women (8% versus 6.8%).

The set of findings regarding the total risk factor count in young men and women is a real strength of paper 4. These results extend previous work relating to the prevalence of CV risk factors in young people by clarifying the absolute number of risks that are really present. This has not been done before and presents a unique method in constructing a risk factor profile based on the WHO framework that carries much weight in terms of risks attributable to CVD. While previous research has shown that interventions can be helpful in targeting CV risks in young people, findings of this paper suggest more work needs to be done at the intervention and clinical level to reduce this risk factor count in young men and women. The real strength of this paper was demonstrating that young people have multiple CV risks, that greatly heighten their risk of CV related illness and death. The finding of overweight and obesity being present in over half of this sample was striking, and suggests that these young people are at risk of being predisposed to other metabolic complications.

Paper 5

The final paper of the thesis was an extension of paper 4, as it applied the risk factor count in a larger sample of 1156 participants and compared the total number of risk factors in younger participants with older participants aged 35-64 years. This paper showed that older men had an average of 4 risk factors, which was higher than younger men who had an average of 3 risk factors. Similarly, older women had an average of approximately 4 risk factors which was also higher than their younger counterparts who had an average of 3 risk factors. This paper was also an investigation into the prevalence of individual risk factors among the younger and

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older age groups. It was found that biomedical risks were more common in older men and women opposed to younger men and women. This paper also highlighted that smoking was more common in younger men than older men; conversely, older male participants had a higher rate of physical inactivity opposed to younger male participants.

Paper 5 was effective in demonstrating that older participants have more CV risk factors than younger participants. This finding suggested that older people are at a heightened risk of CVD. These results also support the contention that CV risks exist at an early age and may progress with increasing age. Paper 5 offered insight into the high prevalence of smoking, particularly among men, that was also reported in paper 4. In line with previous work, this paper showed that apart from obesity, men had a higher prevalence of all CV risk factors than women. This stands in contrast to Lawrence et al (2013), where it was suggested that excess deaths due to CVD were more common in women with schizophrenia compared with their male counterparts. Thus, this paper demonstrated that men and women may have a different presentation of risks affecting CVD outcomes.

Theoretical Implications of Main Findings

The five manuscripts presented in the thesis above, have expanded upon our understanding of the risk factors associated with cardiovascular illness in people with psychotic illnesses. The outcomes of the five papers have very important theoretical and clinical implications. One of the first contributions resulting from the first aim of the thesis was the identification of the national prevalence of people who fail to conform to dietary guidelines. Importantly, the thesis expanded the understanding of those who are most at risk of poor dietary behaviour. That is, men who are aged 18-34 years and use substances are most at risk of eating poorly. In addition, smoking had the strongest influence on poor dietary behaviour. Therefore, it is crucial that smoking is consistently addressed among health care workers that may provide benefits on increasing nutrient intake and thus, reduce the risk of CVD.

Paper 2 delved further into dietary behaviour and showed that the nutrient profile in people with psychosis and the general population are indeed different. Some studies suggest that women with schizophrenia consume more total calories than women controls and this was supported in the thesis as women consumed more vitamins and minerals compared with women in the normal population. The consumption of saturated fat, total fat and sodium in people with psychosis was in excess of recommendations and was greater than population levels. However, the main contribution of paper 2 was highlighting the proportion of people who are above or below the recommended dietary intake for nutrients. Ultimately, this can help health care workers make informed decisions regarding the preparation of dietary plans

by incorporating foods that will support nutrient recommendations. Thus, the thesis provided further support for the contention that people with psychosis are more vulnerable to eating a poorer quality diet compared with the normal population. Paper 3 made a new contribution to the literature by examining pulse pressure (PP) and mean arterial pressure (MAP) using a large sample of people. This paper provided understanding into the factors that are associated with a higher PP and higher MAP. Male gender was another common risk factor for increased PP and MAP. Findings of paper 4 also suggest that older men with a having a family history of hypertension are at greater risk of increased arterial stiffness and greater peripheral resistance. Studies in the general population suggest that lower education, living alone, having diabetes, having obesity and being physically inactive predict a higher PP; while low financial status, obesity and poor diet is predictive of increased MAP. Thus, this paper demonstrated that the health risk factors affecting PP and MAP are different in people with psychosis compared with their healthy peers. However, more research is warranted to investigate why diastolic hypertension is more common than systolic hypertension among people with psychotic illness. Collectively, the first three papers successfully addressed the first aim of the thesis, as they provided information about dietary adherence, blood pressure and their associated risks in a large, representative population of people with psychosis. In doing so, this has broadened the understanding of, and shed light onto the patients' characteristics and behaviours that must be targeted by health professionals in order to reduce the risk of CVD.

The second aim of the thesis was to bring all of the eight risk factors together to determine how many were present in each individual. The proportion of people who have specific CV risks has been previously reported; however there is still no literature about the total number of CV risks. Thus, paper 4 and 5 represent an important contribution to the field of psychiatry in clarifying this unresolved issue. In paper 4, the identification of 2 and 3 risk factors in young women and men aged 18-24 years, respectively, is worrying and supports that contention that young people with psychosis are at greater risk of metabolic issues relative to their healthy peers. Furthermore, these findings offer further support for the argument concerning the excess mortality among people with psychosis. These findings revealed that multiple risk factors already exist at an early age. Lloyd-Jones et al., (2006) theory on multiple CV risks and decreased median survival suggest that young people in this study are already at risk of dying early; therefore, early intervention is strongly warranted. A risk factor count, incorporating the eight WHO-defined risk factors could be used as a framework at the intervention level for assessing whether such interventions have resulted in a reduction in CV risks. Paper 4 provided a clear indication of what risk factors are most common among young participants and therefore, provided awareness of what risk factors

may need to be commonly addressed by health care workers. Paper 5 extended the understanding of the total number of risks in young people, through a comparison of the total number of risks in young men and older women aged 18-34 and 35-64 years, respectively. It was shown that while multiple risks were present in the younger men and women, older men and women had a higher prevalence of CV risks. The findings provide strong evidence that age and the total number of CV risks is positively related.

Methodological Limitations and Future Directions

Like all research projects, the present thesis has a number of methodological limitations. The limitations discussed in the previous chapters have not been repeated here. The sample size used in paper 2 was smaller than the sample size used in paper 1 (i.e. $n = 184$ versus 1286). As a result, the findings from paper 2 may be a reflection of sampling bias and may not have the same degree of generalisability as in paper 1. Another important limitation is the measure of diet inadequacy in paper 1 as this definition does not reflect the WHO definition. Thus, the prevalence of diet inadequacy is an under-estimate of the true prevalence. A small percentage of participants in paper 1 comprised of people without a psychotic diagnosis. Therefore, the findings are not completely reflective of people who have a psychotic illness. The use of antipsychotic medications was not controlled for in papers 1 through to 5, despite a large body of literature highlighting the adverse metabolic side effects and changes in appetite from taking these. Therefore, findings relating to biomedical factors and dietary consumption may have been affected by the pattern of use of some antipsychotic agents. The results in the thesis were based on people accessing public specialised mental health services and did not cover people who were in the private sector or institutionalised. Furthermore, the WHO does not include cannabis as one of the risk factors that contribute to morbidity and mortality as there is insufficient evidence about the impact of cannabis on morbidity and mortality. However, cannabis abuse is very common in people with psychosis, and may impact on CV health (Waterreus et al., 2016). In paper 5, the sample size decreased after stratifying the sample by diagnoses and by those who provided fasting blood samples. This resulted in an unequal sex ratio. Lastly, data on antipsychotic medication was not included in the analyses throughout papers 1 to 5 to determine potential effects of medication use on CV risks. This is in fact, very complicated as participants in this research study, was often taking multiple psychotropic medications (e.g. two antipsychotics, an antidepressant such as mirtazapine, and a mood stabiliser such as sodium valproate), all of which can affect metabolic health. In addition, grouping medication as first and second generation antipsychotics is not helpful as some first generation drugs are associated with weight gain (e.g. chlorpromazine) and the amount of

weight gained from second generation drugs varies considerably (e.g. amisulpride compared with olanzapine). Thus, it was not feasible in this thesis to examine the effect of psychiatric medication upon physical health as longitudinal data is warranted to accurately investigate the effects of antipsychotics drugs on CV health. A more detailed description on antipsychotic medication use among participants in this current study has been published by (Waterreus et al., 2012).

There are a number of future directions that have emerged from this research. Firstly, future work should replicate the findings derived from paper 1, using the WHO definition measuring diet inadequacy. This would provide an accurate representation of dietary intake in accordance with the WHO criteria. Importantly, the risk factor count that was applied in papers 4 and 5 should be extended in future studies with incorporating an algorithm to assess CV risk. For example, identifying the impact of having two risk factors opposed to three risk factors could help determine the short-term or lifetime risk of developing CVD. Moreover, future studies should work on identifying the nature of multiple risks that are present. This could help inform intervention designs as health workers would specifically know the combination of risks to target.

Conclusion

The current thesis was an investigation into cardiovascular (CV) risk factors that are globally recognised to contribute to morbidity and mortality. This research revealed important findings, particularly with respect to the risks associated with poor dietary behaviour, and elevated blood pressure, as well as providing an overall depiction of CV risk factors. The health profile of people with psychosis is very poor and this is further compounded by the interplay between poverty, social exclusion, disadvantage and lack of support. On the positive side, all of the CV risk factors addressed in the present thesis are modifiable, thus cardiovascular disease (CVD) can be prevented. However, it is imperative that psychosis services continue to work hard and provide ongoing, tailored support to improve the physical and mental health of people with severe mental illness.

Appendix B

(Conference Attendance and Presentations)

- The 12th Biennial Australasian Schizophrenia Conference (Melbourne) May 2013
  Speaker presenter - 'Determinants of increased tobacco smoking among people with psychosis living in a disadvantaged region in South Australia'

- The Faculty of Health Sciences Postgraduate Research Conference (Adelaide) September 2013
  Poster and speaker presenter - 'Determinants of increased tobacco smoking among people with psychosis living in a disadvantaged region in South Australia.'

- The International Society for Nutritional Psychiatry Research (ISNPR) (Melbourne) April 2014
  Speaker presenter - 'Associations of poor fruit and vegetable intake among people with psychosis.'

- The Australasian Schizophrenia Conference (Melbourne) September 2015
  Speaker presenter - 'Health risk factors that contribute to morbidity and mortality among young people with psychosis.'

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