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ORIGINAL ARTICLE

Metabolic syndrome in people with a psychotic illness: is cannabis protective?

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Background. Rates of the metabolic syndrome in people with psychotic illness are high. Emerging evidence suggests that cannabis use may have a positive impact on cardiometabolic risk factors in the general population, but little is known about its impact for people with psychotic illness. Our aim was to investigate whether the rate of the metabolic syndrome in people with psychotic illness was associated with frequency of cannabis use.

Method. The 2010 Australian psychosis survey used a two-phase design to randomly select a nationally representative sample of 1825 adults with psychotic illness for interview and physical assessment. This study is based on 1813 participants who provided data on cannabis use. Multiple logistic regression was used to model the influence of frequency of cannabis use on the metabolic syndrome, adjusting for potential covariates including antipsychotic medication use, smoking, alcohol use and cognitive function.

Results. One-third (33.0%) of participants had used cannabis in the past year. The proportion of non-users, occasional users and frequent users with the metabolic syndrome was 63.0, 51.7 and 43.5%, respectively ($p < 0.001$). In unadjusted analyses, both occasional use and frequent cannabis use were associated with significantly lower odds of the metabolic syndrome. In the adjusted analyses, the association between the metabolic syndrome and frequent cannabis use remained significant [odds ratio = 0.56, 95% confidence interval (CI) 0.39–0.80], but not the association with occasional use (odds ratio = 0.75, 95% CI 0.49–1.13).

Conclusions. While cannabis use may be detrimental for mental health, these data suggest that it may also have a cardiometabolic protective effect. Further investigation is required to understand the mechanism underlying this paradoxical finding.

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Key words: Cannabis, cardiometabolic risk, metabolic syndrome, psychosis.

Introduction

It is well documented that people with a psychotic illness often have poor physical health and a life expectancy reduced by up to 20 years compared with the general population (Lawrence *et al*. 2003; Saha *et al*. 2007; Laursen, 2011). There is also increasing evidence that they are at increased risk of the metabolic syndrome compared with the general population: rates ranging from 40.9 to 54.8% have been reported (Saari *et al*. 2005; McEvoy *et al*. 2005; John *et al*. 2009; Galletly *et al*. 2012). The metabolic syndrome confers double the risk of developing cardiovascular disease and a 5-fold increase in risk for type 2 diabetes mellitus (Alberti *et al*. 2009). The relationship between psychotic illness and metabolic dysregulation is a complex one. A number of modifiable lifestyle risk factors including physical inactivity, a diet low in vegetables and fruit and high in saturated fats, antipsychotic medication and smoking may be contributory factors (Park *et al*. 2003; Correll *et al*. 2006).

To date, little attention has been paid to the role that cannabis may play in the metabolic syndrome in people with a psychotic illness. This is an important area for investigation as rates of past-year cannabis use in this group are high (Green *et al*. 2005), with recent

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Australian findings reporting that 30.8% of people with psychosis had used cannabis in the previous 12 months (Morgan *et al*. 2014). Of interest is the evidence emerging from general population studies showing the positive impact that cannabis may have on cardiometabolic risk factors of users compared with non-users: lower levels of fasting glucose and insulin, lower prevalence of diabetes, smaller waist circumference and body mass index (BMI) and higher levels of high-density lipoproteins (HDLs) (Smit & Crespo, 2001; Hayatbakhsh *et al*. 2010; Le Strat & Le Foll, 2011; Rajavashisth *et al*. 2012; Penner *et al*. 2013). These findings support literature from as early as 1940 which noted that chronic users of more potent cannabis lost weight (Chopra & Chopra, 1940) and in 1981, chronic cannabis users were shown to have lower blood pressure than non-users (Singh *et al*. 1981). However, these results have not been found consistently (Rodondi *et al*. 2006; Muniyappa *et al*. 2013).

The second Australian national survey of psychosis – the Survey of High Impact Psychosis (SHIP) – provided a unique opportunity to examine the relationship between cannabis use and cardiometabolic risk factors in a large, representative sample of people with a psychotic illness. Our aim was to investigate whether rates of the metabolic syndrome in people with a psychotic illness differed depending on their frequency of cannabis use.

Method

Study population

The SHIP was conducted within seven catchment sites across five Australian states, covering a population of some 1.5 million people aged 18–64 years, approximately 10% of the Australian population in this age group. Its main aims were to estimate the treated prevalence of psychosis for people aged 18−64 years and to describe the characteristics and use of services by people with a psychotic illness including but not limited to their cognitive, physical health and substance use profiles (Morgan *et al*. 2012). A two-phase design was used. In phase 1, screening for psychosis took place in public specialized mental health services and in non-government organizations supporting people with a mental illness in the census month (March 2010). A psychosis screener developed for the first national psychosis survey was used to identify individuals likely to meet criteria for formal diagnosis (Jablensky *et al*. 2000). Administrative records were scanned to identify people with a recorded diagnosis of psychosis and in contact with public specialized mental health services in the 11 months prior to census but not in the census month. In phase 2, 1825 people who were screen positive for psychosis in phase 1 were randomly selected, stratified by catchment site and age group, for interview and assessment between April 2010 and April 2011. The present study is based on data on 1813 participants who provided information on their cannabis use. The study was approved by human research ethics committees at each of the seven catchment sites. The full details of the survey methodology and inclusion criteria have been published elsewhere (Morgan *et al*. 2012, 2014).

Assessments

Past-year cannabis use

Participants were classified into three cannabis groups (non-user, occasional user, frequent user) based on responses to a series of questions on self-reported frequency of cannabis use in the previous 12 months. Non-users had not used cannabis in the previous 12 months. Occasional users reported using cannabis less than once per week in the previous 12 months and frequent users had used cannabis at least once per week in the previous 12 months. No distinction was made between the route of cannabis administration (smoking or ingestion), the part of the plant used, nor potency. Information on daily quantity was collected, but as we were unable to quantify these data reliably this was not included in the analyses.

Biochemical and physical health

Interviewers measured blood pressure, height, weight and waist circumference. A fasting blood sample was collected with participants fasting for at least 8 h. Blood samples were taken at accredited pathology laboratories for assays of HDL, triglycerides and plasma glucose. The World Health Organization BMI reference range was used to classify participants as obese ($\geqslant 30\ kg/m^2$), overweight ($25–29\ kg/m^2$) or underweight/normal ($<25\ kg/m^2$) (World Health Organization, 2000).

The metabolic syndrome was defined using the International Diabetes Federation harmonized criteria: participants had to meet the threshold for at least three of the five components (waist circumference, blood pressure, triglycerides, glucose and HDL) or be prescribed medication for hypertension, hyperlipidaemia or hyperglycaemia. The recommended cut points for waist circumference for Europid and non-Europeans were used (Alberti *et al*. 2009). Participants were identified as having diabetes if they had fasting plasma glucose of at least 7.0 mmol/l, were currently taking anti-diabetic medication, or answered yes to the question 'Do you have diabetes or have you been told your blood sugars are high?'. It was not possible to distinguish between type 1 and type 2 diabetes. Full details of assessment procedures are provided in the online supplementary files to Morgan *et al*. (2014).

Psychopathology, cognition and lifestyle

Classification of psychotic illness according to International Classification of Diseases (ICD)-10 criteria was made using the Diagnostic Interview for Psychosis (Castle *et al*. 2006) a semi-structured clinical interview with questions and probes derived and adapted from the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (Wing *et al*. 1990). The Diagnostic Interview for Psychosis has good reliability and validity and its psychometric properties have been established.

Physical activity undertaken in the 7 days prior to interview was measured using the interviewer-administered International Physical Activity Questionnaire short form (Craig *et al*. 2003). Activity was categorized into three levels (low, moderate or high) using scoring guidelines. Dietary intake over the previous 4 weeks was assessed using a series of questions on the consumption of fruit, vegetables and caffeinated drinks, among others. Participants were asked 'How many serves of fruit/vegetables do you usually eat each day?' One serve of fruit was the equivalent of one medium piece, two small pieces or one cup of diced fruit. Half a cup of cooked vegetables or one cup of salad vegetables was one serve. A list of caffeinated drinks was shown to each participant and they were asked 'How many of these would you drink on average per day?'. This was converted to a total caffeine intake in mg per day.

The 10-item Alcohol Use Disorders Identification Test (AUDIT; Saunders *et al*. 1993) was administered and the derived AUDIT-C score (Bush *et al*. 1998) was calculated from the responses to the first three questions related to alcohol consumption in the previous year. A score of three or more for women and four or more for men was used to identify hazardous drinking in the previous year. Smokers were defined as anyone who reported smoking tobacco in the 4 weeks prior to interview. Participants were asked about the frequency and quantity of illicit drugs used, including cannabis and amphetamines. Lifetime and previous 12-month use was recorded separately for each drug. Antipsychotic medication use over the 4 weeks prior to interview was based on self-report or review of medication charts.

The Digit Symbol Coding Test from the Repeatable Battery for the Assessment of Neuropsychological Status (Randolph *et al*. 1998) assessed current cognitive processing efficiency. Raw scores were grouped into terciles, with a fourth category covering those who did not complete the task.

Socio-economic status (SES) was categorized using Australian Bureau of Statistics Socio-Economic Indexes for Areas based on postcode of residence at the time of interview (Australian Bureau of Statistics, 2008). We used the Index of Relative Socio-Economic Disadvantage expressed in quintiles, with the lowest quintile representing the greatest disadvantage.

Statistical analysis

Descriptive statistics were employed to summarize key variables used in the analyses according to the three cannabis groups. Sample weights were used to correct for differential selection probabilities and were incorporated into all analyses generating tests of significance. Raw counts are presented for categorical data. Weighted means and standard deviations are presented for continuous variables. Analysis of variance was used to test for differences in means between groups. Univariate logistic regression analyses were used to identify strengths of association between the metabolic syndrome and relevant explanatory variables.

Multiple logistic regression was used to model the influence of cannabis use upon meeting the criteria for the metabolic syndrome while simultaneously accounting for the effects of all other relevant influences present. Variables considered as possible confounders, mediators or moderators were sex, age, SES, ICD-10 diagnosis, smoking status, alcohol use, amphetamine use, level of physical activity, cognitive function, antipsychotic medication use, fruit and vegetable consumption and caffeine intake. To determine which of these variables were necessary to retain in a final adjusted model, a combination of techniques was used. Where the odds ratios for the categories of cannabis use changed by more than 10% after the subsequent inclusion of additional explanatory covariates, those covariates were identified for inclusion. Sex, age and SES were included in the multiple logistic regression because of their importance as core epidemiological adjustment variables. All other variables included in the final model had contributed significantly to explaining the variability in meeting metabolic syndrome criteria across participants and/or caused substantial changes in the odds ratios for cannabis use by their inclusion in the model. The final model included cannabis use, sex, age, SES, ICD-10 diagnosis, smoking status, alcohol use, level of physical activity, cognitive function and use of antipsychotic medication. Neither BMI nor diabetes was included in the modelling due to their close association with components of the metabolic syndrome. We reported the odds ratios and 95% confidence intervals (CIs) of all retained covariates. Participants with a missing value for any covariate used in the final model were excluded from that analysis ($n = 1311$ in final model).

To complement our analysis, we determined prevalence ratios using weighted Poisson regression, given that odds ratios are not precise estimates of prevalence ratios when prevalence rates are relatively high. In addition, to supplement the rigour of the logistic regression analysis, we also undertook propensity score analysis using a dichotomized version of our cannabis use variable: we investigated differences in rates of the metabolic syndrome between users and non-users of cannabis using (i) a reduced sample of participants where cannabis users and non-users were matched on their propensity scores and (ii) the propensity scores to adjust for possible confounding. Data were analysed using SPSS 21 (USA) and STATA v. 13 (USA).

Results

Cannabis use

The demographic and clinical profiles of the 1813 participants who had provided data on their cannabis use are summarized in Table 1. The majority of participants (89.9%) met ICD-10 criteria for a psychotic disorder, with 46.8% having a diagnosis of schizophrenia. Lifetime cannabis use was common (66.9%) whilst, in the preceding 12 months, one-third (33.0%) of participants reported using cannabis. Among users, 70.1% were male and 55.9% were aged 18–34 years. The proportion of participants in each cannabis group did not differ by diagnostic group or by SES level. Of the 598 participants using cannabis in the previous 12 months, 41.5% were classified as occasional users and 58.5% as frequent users. Despite the fact that cannabis use was more common in younger people, two-thirds (65.2%) of people aged 45 years or older using cannabis were classed as a frequent user.

Metabolic syndrome and its components

A total of 1345 participants had sufficient measurements to determine the metabolic syndrome. Those for whom the metabolic syndrome could not be determined did not differ by sex, cannabis or alcohol use but were more likely to be younger than participants with a full suite of measurements. The overall prevalence of the metabolic syndrome was 57.8%. The proportion of cannabis non-users, occasional users and frequent users with the metabolic syndrome was 63.0, 51.7 and 43.5%, respectively ($p < 0.001$). In unadjusted analyses occasional use and frequent cannabis use were associated with significantly lower odds of the metabolic syndrome (Table 2).

Abdominal obesity assessed using waist circumference was the most commonly met criterion for the metabolic syndrome, being found in 82.4% of participants. Waist circumference was also the criterion which best differentiated the three cannabis groups. The weighted mean waist circumference for frequent users was on average 8.8 cm smaller than non-users [100.1 (S.D. = 17.5) cm compared with 108.9 (S.D. = 18.8) cm, $p < 0.001$]. Over half the participants met the thresholds for hypertension, triglycerides and HDL (52.7, 53.5 and 57.0%, respectively). The proportion meeting each of the five metabolic syndrome criteria decreased with increasing cannabis use, as shown in Table 3. Relative to non-users, the odds of all five criteria were reduced in frequent users (Fig. 1).

Modifiable lifestyle risk factors

Lifestyle factors such as smoking tobacco, physical inactivity and alcohol consumption may confound the relationship between cannabis and the metabolic syndrome. Many participants had been exposed to such risk factors (see Table 1). Almost half (47.0%) had low physical activity levels; 12.5% had not engaged in any physical activity in the previous 7 days. Participants taking part in high levels of physical activity were at lower risk of the metabolic syndrome than those with no or low levels of activity. There was a trend-level association between participants' frequency of cannabis use and level of physical activity ($p = 0.07$). Two-thirds (66.7%) of all participants but almost all (91.6%) cannabis users smoked tobacco. Smokers were at increased risk of the metabolic syndrome compared with non-smokers. Many participants (44.7%) were engaging in high-risk drinking and there was a difference in the proportion of participants reporting this behaviour across the three cannabis groups ($p < 0.001$) (see Table 1). Participants with heavy alcohol intake had higher mean HDL concentrations than those drinking lower amounts/non-drinkers (1.22 mmol/l compared with 1.15 mmol/l, unadjusted $p = 0.04$); they were also at a lower risk of the metabolic syndrome (adjusted odds ratio = 0.74, 95% CI 0.56–0.97). Few participants met daily recommended dietary guidelines; 71.7% reported eating one serve or less of fruit per day and 48.8% had one serve or less of vegetables per day. The majority of participants (81.6%) were receiving antipsychotic medication but fewer frequent cannabis users were using clozapine than occasional and non-users ($p < 0.001$). Participants using antipsychotic medication (excluding clozapine) were at an increased risk of having the metabolic syndrome compared with those not using an antipsychotic. This risk was even higher for those using clozapine.

Cognition

Mean cognitive function was similar across the three cannabis groups [non-user 38.4 (S.D. = 11.2), occasional

Table 1. *Demographics and clinical characteristics of the sample population according to past-year cannabis use*

	Total sample		Frequency of cannabis use								
	(*n* = 1813)		None (*n* = 1215)		Occasional (*n* = 248)		Frequent (*n* = 350)		Analysis[a]		
	n	%	*n*	%	*n*	%	*n*	%	χ^2	df	*p*
Metabolic syndrome[b]									30.6	2	<0.001
No	567	42.2	338	37.0	85	48.3	144	56.5			
Yes	778	57.8	576	63.0	91	51.7	111	43.5			
Age, years									129.0	8	<0.001
18–24	200	11.0	103	8.5	39	15.7	58	16.6			
25–34	566	31.2	329	27.1	99	39.9	138	39.4			
35–44	493	27.2	321	26.4	78	31.5	94	26.9			
45–54	385	21.2	309	25.4	26	10.5	50	14.3			
55–64	169	9.3	153	12.6	6	2.4	10	2.9			
Sex									44.8	2	<0.001
Male	1078	59.5	659	54.2	166	66.9	253	72.3			
Female	735	40.5	556	45.8	82	33.1	97	27.7			
ICD-10 diagnosis									4.6	10	N.S.
Schizophrenia	849	46.8	567	46.7	121	48.8	161	46.0			
Schizo-affective	292	16.1	186	15.3	44	17.7	62	17.7			
Bipolar disorder with psychotic features	318	17.5	216	17.8	39	15.7	63	18.0			
Depressive psychosis	81	4.5	53	4.4	14	5.6	14	4.0			
Delusional disorders and other non-organic psychosis	90	5.0	63	5.2	10	4.0	17	4.9			
Other	183	10.1	130	10.7	20	8.1	33	9.4			
Antipsychotic use									42.3	4	<0.001
No	333	18.4	208	17.1	53	21.4	72	20.6			
Yes, but not clozapine	1184	65.3	765	63.0	160	64.5	259	74.0			
Yes, clozapine	296	16.3	242	19.9	35	14.1	19	5.4			
Tobacco use[c]									235.6	2	<0.001
Current smoker	1202	66.7	658	54.4	221	90.2	323	92.6			
Alcohol use[d]									202.4	2	<0.001
Hazardous drinking	805	44.7	397	32.9	171	69.5	237	67.9			
Physical activity[e]									8.6	4	0.072
Low	853	47.7	588	49.1	126	51.4	139	40.1			
Moderate	677	37.8	447	37.3	82	33.5	148	42.7			
High	259	14.5	162	13.5	37	15.1	60	17.3			
Socio-economic status[f]									9.7	8	N.S.
1 Most disadvantaged	360	19.9	232	19.1	48	19.4	80	22.9			
2	365	20.2	263	21.7	35	14.2	67	19.2			
3	351	19.4	232	19.1	58	23.5	61	17.5			
4	372	20.6	242	19.9	58	23.5	72	20.6			
5 Least disadvantaged	362	20.0	245	20.2	48	19.4	69	19.8			
Cognitive function									13.7	6	0.03
Middle tercile	503	27.7	319	26.3	72	29.0	112	32.0			
Lowest tercile	527	29.1	366	30.1	66	26.6	95	27.1			
Highest tercile	582	32.1	383	31.5	83	33.5	116	33.1			
Did not do task	201	11.1	147	12.1	27	10.9	27	7.7			
Diet[g]											
>1 serve/day – vegetables	920	51.2	677	56.2	98	40.2	145	41.7	35.4	2	<0.001
>1 serve/day – fruit	509	28.3	405	33.6	45	18.4	59	17.0	46.6	2	<0.001
Diabetes									22.8	2	<0.001
Yes	401	22.1	307	25.3	43	17.3	51	14.6			

Table 1 (*cont.*)

	Total sample		Frequency of cannabis use								
	(n = 1813)		None (n = 1215)		Occasional (n = 248)		Frequent (n = 350)		Analysis[a]		
	n	%	n	%	n	%	n	%	χ^2	df	p
BMI[h]									95.4	4	<0.001
Underweight/normal	431	24.4	223	19.0	73	29.8	135	39.1			
Overweight	514	29.1	321	27.3	82	33.5	111	32.2			
Obese	819	46.4	630	53.7	90	36.7	99	28.7			

df, Degrees of freedom; ICD, International Classification of Diseases; n.s., non-significant; BMI, body mass index.
[a] We report unweighted n and percentages but weighted p values.
[b] 468 participants with insufficient measures.
[c] 10 participants without information.
[d] 12 participants without information.
[e] 24 participants without information.
[f] Three participants without information.
[g] 16 participants without information.
[h] 49 participants without information.

user 39.4 (S.D. = 10.3), frequent user 39.1 (S.D. = 9.4)]; all groups scored well below the population mean [54.2 (S.D. = 9.8)] (Australian Schizophrenia Research Bank, 2011).

Multiple logistic modelling

The final multiple logistic regression model contained variables identifying cannabis use, sex, age, SES, ICD-10 diagnosis, smoking status, alcohol use, level of physical activity, cognitive function and use of antipsychotic medication. The relevant odds ratios and 95% CIs for all variables can be found in Table 2. In the adjusted analysis, frequent cannabis users remained at significantly lower odds for the metabolic syndrome compared with non-users (adjusted odds ratio = 0.56, 95% CI 0.39–0.80). Occasional users also had a lower odds ratio than non-users but this was not statistically significant (adjusted odds ratio = 0.75, 95% CI 0.49–1.3). A number of other risk factors were independently associated with the metabolic syndrome (see Table 2).

Poisson regression

When modelling the metabolic syndrome as a Poisson outcome explained by cannabis use and the same set of covariates used in the logistic regression analysis, the rate ratio (RR) for frequent cannabis users compared with non-users was estimated to be 0.79 (95% CI 0.67–0.92). The RR for occasional users compared with non-users was not significantly different from 1 (RR = 0.91, 95% CI 0.77–1.08). RR estimates for all other explanatory covariates are presented in online Supplementary Table S1.

Propensity score analysis

In a reduced sample analysis where only participants matched on propensity scores were retained, we observed the odds ratio of having the metabolic syndrome for cannabis users relative to non-users was significant (odds ratio = 0.574, 95% CI 0.397–0.829). In a multiple logistic regression where meeting the metabolic syndrome criteria was modelled as a function of cannabis use in the past year (yes/no) with adjustment for the propensity score, a significant effect of cannabis use was observed (odds ratio = 0.648, 95% CI 0.477–0.881). Details of propensity score calculation and matching are presented in online Supplementary Table S2.

Diabetes and obesity in cannabis users

Diabetes and BMI were examined separately to assess differences across the three cannabis groups. Almost one in four (22.1%) participants had diabetes, and, of these, 76.6% were non-users, 10.7% occasional users and 12.7% frequent users. The difference in percentage of cannabis users between those with and without diabetes was significant (p < 0.001). Three-quarters (75.6%) of all participants were classified as overweight or obese and the mean overall weighted BMI was 30.5 (S.D. = 7.5) kg/m^2. More than half (53.7%) of the non-users were obese compared with 36.7% of occasional and 28.7% of frequent users (p < 0.001).

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Table 2. *Odds ratios (unadjusted and adjusted) for cannabis use and other variables in predicting the metabolic syndrome*

Variable	Unadjusted – bivariate analysis	Adjusted simultaneously for all listed variables
Cannabis use		
None	Reference	Reference
Occasional	0.64 (0.46–0.91)	0.75 (0.49–1.13)
Frequent	0.46 (0.34–0.62)	0.56 (0.39–0.80)
Age	1.04 (1.03–1.05)	1.03 (1.02–1.04)
Sex		
Female	Reference	Reference
Male	0.97 (0.76–1.22)	0.97 (0.74–1.29)
Diagnosis		
Schizophrenia	Reference	Reference
Schizo-affective	1.26 (0.90–1.75)	1.54 (1.07–2.23)
Bipolar disorder with psychotic features	1.50 (1.08–2.08)	2.16 (1.48–3.15)
Depressive psychosis	0.78 (0.46–1.33)	1.39 (0.77–2.49)
Delusional disorder[a]	1.17 (0.68–2.02)	1.59 (0.89–2.86)
Other	0.58 (0.39–0.86)	0.97 (0.59–1.57)
Antipsychotic use		
No	Reference	Reference
Yes, but not clozapine	2.12 (1.55–2.90)	1.73 (1.20–2.49)
Yes, including clozapine	4.52 (2.97–6.87)	4.41 (2.67–7.27)
Current smoker		
No	Reference	Reference
Yes	1.27 (1.00–1.61)	1.65 (1.22–2.24)
Alcohol risk		
No	Reference	Reference
Hazardous drinking	0.59 (0.46–0.74)	0.74 (0.56–0.97)
Physical activity		
Low	Reference	Reference
Moderate	0.79 (0.61–1.01)	0.81 (0.62–1.07)
High	0.37 (0.26–0.52)	0.49 (0.33–0.73)
Socio-economic status	1.00 (0.99–1.00)	1.00 (1.00–1.00)
Cognitive function		
Middle tercile	Reference	Reference
Lowest tercile	1.18 (0.87–1.60)	0.85 (0.61–1.20)
Highest tercile	0.51 (0.38–0.68)	0.54 (0.39–0.76)
Did not complete	0.70 (0.45–1.09)	0.51 (0.31–0.83)

Data are given as odds ratio (95% confidence interval).
[a] Includes other non-organic psychoses.

Discussion

This study examined the relationship between frequency of cannabis use and the metabolic syndrome in a large population-based sample of people with psychosis. Participants who reported using cannabis in the previous 12 months were significantly less likely than non-users to have the metabolic syndrome. This association remained significant for frequent users (using at least once per week in the previous 12 months) after adjustment for a range of potential confounders, including lifestyle, cognitive function, antipsychotic use, diagnosis and sociodemographic characteristics. For occasional users using cannabis less than once per week in the previous 12 months, the adjusted odds ratio was still reduced but no longer significant.

We found that frequent cannabis users were significantly less likely to meet each of the five metabolic syndrome criteria than participants reporting no cannabis use. An association was also found with cannabis use and criteria for waist circumference, glucose and hypertension in occasional users which may suggest that the effect that cannabis has on some cardiometabolic risk factors does not require more sustained use.

In this representative sample of people with a psychotic illness, the rate of past-year cannabis use was high,

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Table 3. *Frequency of the individual components of the metabolic syndrome according to the use of cannabis*

	Frequency of cannabis use											
	Non-user		Occasional		Frequent		Analysis[a]		Occasional compared with non-user		Frequent compared with non-user	
Met metabolic syndrome risk threshold	n	%	n	%	n	%	χ^2 (df = 2)	p	Adjusted OR	95% CI	Adjusted OR	95% CI
Waist circumference	1014	87.0	201	82.7	229	66.6	75.0	<0.001	0.68	0.46–1.01	0.29	0.21–0.39
HDL	533	59.4	97	56.1	126	49.2	8.5	0.014	0.95	0.60–1.34	0.68	0.51–0.92
Hypertension	662	56.3	116	47.5	150	44.0	21.3	<0.001	0.72	0.54–0.96	0.58	0.45–0.75
Triglycerides	516	57.1	85	48.3	114	44.5	15.1	0.001	0.75	0.53–1.06	0.61	0.45–0.83
Glucose	329	37.0	47	26.6	62	24.5	17.8	<0.001	0.59	0.40–0.88	0.60	0.43–0.85

df, Degrees of freedom; OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein.
[a] We report unweighted n and percentages but weighted p values.

at 33.0%; much higher than the 9% reported for the Australian general population (Roxburgh *et al*. 2010). There is evidence, although inconclusive, that cannabis use is associated with poorer clinical outcomes for people with psychotic illness (Barrowclough *et al*. 2015) and cognitive decline (Meier *et al*. 2012) and increased respiratory symptoms (Tetrault *et al*. 2007) in general population samples. In light of this, the finding that frequent cannabis use reduces the risk of the metabolic syndrome is challenging and the potential mechanisms underlying its action need to be understood.

A numbers of studies have examined the association between cannabis use and cardiometabolic risk factors including studies using treatment with CB_1 receptor blockers (Smit & Crespo, 2001; Després *et al*. 2005; Van Gaal *et al*. 2005; Cota *et al*. 2009; Le Strat & Le Foll, 2011; Penner *et al*. 2013). With a few exceptions (Rodondi *et al*. 2006; Muniyappa *et al*. 2013), results seem to show that cannabis and CB_1 receptor blockers have a significant impact on reducing body weight, fasting plasma glucose, blood pressure and waist circumference, suppressing appetite and increasing adiponectin and HDL-cholesterol. The results of our study add further weight to this evidence.

The endocannabinoid pathways are an extremely complex signalling system which regulates energy metabolism and body weight in ways not yet fully understood (Pagotto *et al*. 2006). The system is comprised of endocannabinoids and cannabinoid receptors (CB_1 and CB_2) expressed centrally in the hypothalamus and peripherally in tissues including the liver, pancreas, gastrointestinal tract, immune cells and adipose tissue and is thought to function by regulating levels of endocannabinoids and by altering cannabinoid receptor activity. Dysregulation and over-activation of the endocannabinoid system may contribute to excessive energy stored as fat, insulin resistance and dyslipidaemia through the inhibition of adiponectin production and interference with adipocyte biology (Di Marzo, 2008; Teixeira *et al*. 2010). Cannabinoids, particularly tetrahydrocannabinol (THC), the main psychoactive component in cannabis, have been reported to mimic the action of endocannabinoids (Pertwee, 2008). Importantly THC has been shown to act as a CB_1 and CB_2 receptor antagonist as well as agonist (Pertwee, 2008). In addition to THC, cannabis comprises more than 60 different cannabinoids including cannabidiol (CBD) and tetrahydrocannabivarin (THCV) which have both been shown *in vivo* to have therapeutic metabolic effects (Weiss *et al*. 2006; Wargent *et al*. 2013). It has been suggested that THC, THC/CBD or CBD/THCV combination drugs may be beneficial in the treatment of diabetes, the metabolic syndrome and obesity (Le Foll *et al*. 2013; Wargent *et al*. 2013). Cannabinoids may also regulate

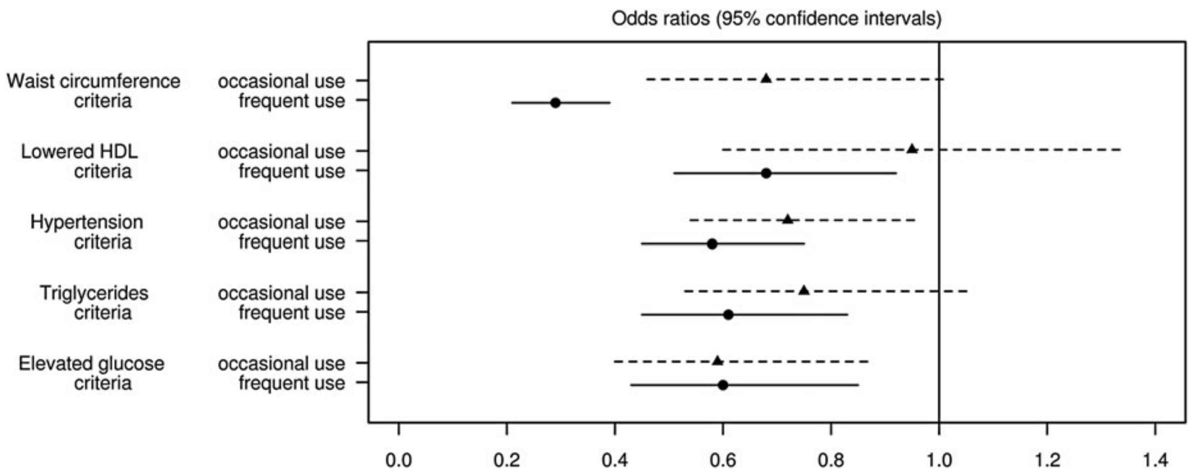

Fig. 1. Odds ratios and 95% confidence intervals for individual components of the metabolic syndrome according to the frequency of cannabis use relative to no use. HDL, High-density lipoprotein.

metabolism through activating other nuclear receptors including peroxisome proliferator-activated receptors (PPARs) (Teixeira *et al*. 2010). Cannabis also contains flavonoids, which even in small amounts may mitigate the risk factors for the metabolic syndrome (Galleano *et al*. 2012; McCullough *et al*. 2012).

Short-term use of cannabis activates CB_1 receptors and induces acute transient effects including increased blood pressure and appetite. It has been suggested that regular 'chronic' cannabis use may induce tolerance with receptor down-regulation, desensitization, and a reduction in density and signalling efficiency as well as altering levels of endocannabinoids (Lichtman & Martin, 2005; D'Souza *et al*. 2008; Hirvonen *et al*. 2011; Ceccarini *et al*. 2015). This difference in effects from short-term and chronic use may explain discrepancies between studies as each used differing criteria to classify cannabis users. In the current study, which focuses on cannabis use over a period of 12 months, we found that the positive effects of cannabis use were greater for frequent users compared with occasional users. It is known that THC is stored in fat cells and can be slowly released over days and weeks (Gunasekaran *et al*. 2009), which may explain why cannabis can maintain its therapeutic effect days or weeks after last being used.

Strengths and limitations

The strength of our study lies in its sampling design which ensured that our findings are generalizable to adults with a broad spectrum of psychotic disorders in contact with public mental health services. Additionally, the use of biochemical and standardized anthropometric measurements collected at the time of interview by trained health professionals ensured that our physical health assessments were well calibrated as they did not rely on self-reported or retrospective measures. Several limitations should also be considered. First, this is a cross-sectional study: longitudinal data are needed to confirm the direction of causality in the association found. Second, information gathered on cannabis use was based on self-report so there may have been a recall bias with users underestimating the frequency of use, giving socially desirable responses or denying use. To minimize this potential bias, no participant was interviewed by a researcher who had been directly involved in providing mental health care to them. Third, the variability in potency of cannabis used may play a role and this was not assessed. Finally, not all participants provided fasting blood samples. Whilst no differences were found in terms of age, sex or cannabis and alcohol use between those who did and those who did not provide fasting samples, there may have been an undetected bias.

Conclusions

Poor physical health compounds the heavy burden already associated with psychotic illness. The challenge is to treat both the mental and physical health of these people, a challenge made more complex by the high rates of illicit drug and alcohol use in this population. On one hand, cannabis has reportedly detrimental effects on the mental health of people with psychotic illness but, on the other hand it has an apparent cardiometabolic protective effect. Further investigation is required to understand this paradoxical action of cannabis. The complex endocannabinoid system remains to be fully understood, as does the role played by individual cannabinoids and how they exert their effects on different metabolic pathways. Alternatively, cannabis may be a proxy for some as yet unidentified factor. Despite the results of our study, it is premature to conclude that people with a psychotic illness should be advised to use cannabis as a mode for offsetting their risk of cardiometabolic disease.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715002883

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Declaration of Interest

None.

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