Drug and Alcohol Dependence 194 (2019) 447–452

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

# Sex differences in the cardiometabolic health of cannabis users with a psychotic illness

Anna Waterreus[a,*], Patsy Di Prinzio[a], Mathew T. Martin-Iverson[b], Vera A. Morgan[a,c]

[a] Neuropsychiatric Epidemiology Research Unit, Division of Psychiatry, Medical School, University of Western Australia, Perth, Australia
[b] Pharmacology, School of Biomedical Sciences, University of Western Australia, Perth, Australia
[c] Centre for Clinical Research in Neuropsychiatry, Division of Psychiatry, Medical School, University of Western Australia, Perth, Australia

ARTICLE INFO

*Keywords:*
Cannabis
Sex
Cardiometabolic
Psychosis

ABSTRACT

Background: Growing evidence shows cannabis use is associated with lower rates of metabolic dysregulation. Despite cannabis impacting each sex differently, few studies have examined the metabolic profile of male and female cannabis users separately. Our aim was to investigate sex differences in the impact of cannabis use on metabolic syndrome in adults with psychotic illness.

Method: Data from 1078 men and 735 women interviewed in the second Australian national survey of psychosis were analyzed using multiple logistic regression to model separately, for each sex, the influence of no, occasional and frequent past-year cannabis use on metabolic syndrome, adjusting for potential covariates including antipsychotic medication, smoking, and physical activity.

Results: The proportion of women and men with metabolic syndrome was 58.1% and 57.6% respectively. Unadjusted analyses showed frequent cannabis use was associated with significantly lower odds of metabolic syndrome for both sexes. In adjusted analyses, the association between metabolic syndrome and frequent cannabis use remained significant for men (AOR = 0.49, 95% CI = 0.31-0.78), but not for women (AOR = 0.68, 95% CI = 0.37–1.24). Frequent cannabis use was associated with lower odds of abdominal obesity, hypertension and elevated triglyceride levels in men only.

Conclusions: The differences we found suggest cannabinoid regulation of energy balance may be sex-dependent and highlight the importance of examining cannabis use in men and women separately. At the same time, the negative association between cannabis and psychosis onset and relapse should not be dismissed.

## 1. Introduction

Globally, cannabis is the most used illicit drug (United Nations Office on Drugs and Crime, 2015). With a worldwide trend towards legalizing cannabis, it is expected that the number of people using it will rise, making it increasingly important to better understand the health impacts associated with regular cannabis use. Although the acute effects of cannabis are known and have been well-documented, much of the literature on the effects of chronic use remains inconsistent. There is, however, a growing body of evidence from adult general population and mental health samples showing that cannabis use is associated with better cardiometabolic health (Bruins et al., 2016; Hayatbakhsh et al., 2010; Le Strat and Le Foll, 2011; Liemburg et al., 2016; Ngueta et al., 2015; Penner et al., 2013; Rajavashisth et al., 2012; Scheffler et al., 2018; Vidot et al., 2016; Waterreus et al., 2016). In particular, cannabis users have been shown to have smaller waist circumferences and a lower body mass index than non-users (Moreira et al., 2018). Our previous research on a representative sample of people with a psychotic disorder found the mean waist circumference of frequent users was 8.8 cm smaller than non-users. We also observed the proportion of participants meeting the threshold for elevated glucose, blood pressure, and triglycerides and reduced high-density lipoprotein (HDL) all decreased with increasing frequency of cannabis use (Waterreus et al., 2016).

While an increasing number of animal studies have investigated sex differences in cannabis induced-effects including its impact on the endocannabinoid system (Calakos et al., 2017; Craft et al., 2013; Fattore and Fratta, 2010; Ketcherside et al., 2016), few studies of cannabis in humans have examined sex differences. Wetherington (2007) argues that by omitting to stratify results by sex risks drawing erroneous

* Corresponding author at: Neuropsychiatric Epidemiology Research Unit, Division of Psychiatry, Medical School, University of Western Australia, Level 3 MRF Building, rear 50 Murray St., Perth WA 6000, Australia.
*E-mail address:* anna.waterreus@uwa.edu.au (A. Waterreus).

https://doi.org/10.1016/j.drugalcdep.2018.11.006
Received 18 September 2018; Received in revised form 22 October 2018; Accepted 4 November 2018
Available online 22 November 2018

conclusions including reporting that an effect exists for everyone when it exists for only one sex or finding there is no effect when it exists for one sex only. Two general population studies which have examined the cardiometabolic profile of male and female cannabis users and non-users separately (Moreira et al., 2018; Thompson and Hay, 2015); both reported significantly lower body mass index and waist circumference in current cannabis users compared to non-users for their samples as a whole, but when analyses were stratified by sex, significant effects remained for male cannabis users only.

Despite high rates of past-year cannabis use by men and women with a psychotic illness (Green et al., 2005), we are unaware of any studies investigating sex differences in the cardiometabolic profile of cannabis users in people with psychotic disorders. With Wetherington's advice that adopting a sex-based approach to analysis would guard against 'serious conclusion errors' fresh in our minds, we decided to revisit our earlier findings where we reported a significant association between metabolic syndrome and frequent cannabis use (AOR = 0.56, 95% CI 0.39-0.80), but not with occasional use (AOR = 0.75, 95% CI 0.49–1.13) in a nationally representative sample of 1813 men and women with a psychotic disorder.

The aim of the current study was to re-examine the association between metabolic syndrome and cannabis use in a large sample of people with a psychotic illness to determine whether this association varies by sex and to examine sex differences in the impact of cannabis use on the individual components of metabolic syndrome.

## 2. Method

### 2.1. Study population

The Survey of High Impact Psychosis (SHIP) was conducted in 2010 within seven catchment sites in five states across Australia, covering a population of some 1.5 million people aged 18–64 years, approximately 10% of the Australian population in this age group. The main aims were to estimate the treated prevalence of psychosis for people aged 18 − 64 years and to describe their characteristics and use of services. A two-phase design was used. In Phase 1, screening for psychosis took place in public mental health services and non-government organizations supporting people with mental illness in the census month (March 2010). A psychosis screener was used to identify individuals likely to meet criteria for formal diagnosis (Jablensky et al., 2000). In addition, 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 the census month and who resided in the catchment. In Phase 2, people who were screened positive for psychosis were randomly selected, stratified by catchment site and age group (18–34 and 35–64 years), for interview by trained mental health professionals. A total of 1825 participants gave written informed consent and were interviewed: 1813 participants (99.3%) provided data on past-year cannabis use and were included in this current study. The Institutional Human Research Ethics Committees at all sites approved the study. Details of the full survey methodology, assessment procedures, and the previous metabolic study have been published elsewhere (Morgan et al., 2014, 2012; Waterreus et al., 2016).

### 2.2. Assessments

#### 2.2.1. Past year cannabis use

Participants were classified into three groups based the on self-reported frequency of cannabis use in the 12-months prior to the interview. 'Non-users' had never used or not in the past year, 'occasional users' reported using cannabis less than once a week and 'frequent users' had used at least once a week over the past year. No data was available on the potency of cannabis or total duration of use.

#### 2.2.2. Cardiometabolic risk factors

Blood pressure, weight, and waist circumference were measured at the time of interview and fasting blood samples were taken from consenting participants at accredited pathology laboratories for assays of HDL, triglycerides, and plasma glucose. Full details of testing procedures can be found in the supplementary methods in Morgan et al., 2014. The International Diabetes Federation thresholds were used which includes elevated blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg or antihypertensive medication), elevated triglycerides (≥1.7 mmol/l or hypertriglyceridemia medication), elevated fasting glucose (≥5.6 mmol/l or anti-glycaemic medication), lowered HDL (< 1.03 mmol/l for men, < 1.29 mmol/l for women or lipid-lowering medication) and elevated waist circumference including ethnic specific thresholds (≥90 cm or ≥94 cm for men, ≥80 cm for women). The presence of any three of the five risk factors indicated that the criteria for metabolic syndrome had been met (Alberti et al., 2009).

#### 2.2.3. Covariates

The Diagnostic Interview for Psychosis (Castle et al., 2006), a semi-structured clinical interview which uses the OPCRIT computer algorithm (McGuffin et al., 1991) to classify psychotic illness according to ICD-10 criteria, was administered by trained interviewers. 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 for those who did not complete the task. Past-year alcohol use was assessed using the Alcohol Use Disorders Identification Test (Saunders et al., 1993) and the derived AUDIT-C score (Bush et al., 1998) was used to create a binary variable indicating hazardous drinking in the previous 12-months (yes/no). Physical activity undertaken in the previous seven days was measured using the interviewer-administered International Physical Activity Questionnaire short form (Craig et al., 2003) and categorized into three levels (low, moderate or high) using scoring guidelines. Smokers were defined as anyone who reported smoking tobacco in the four weeks prior to the interview. All antipsychotic medication taken for at least the previous four weeks was recorded (Waterreus et al., 2012). Socioeconomic status (SES) was categorized using Australian Bureau of Statistics Socio-Economic Indexes for Areas, Index of Relative Socio-Economic Disadvantage, based on postcode of residence at the time of interview (Australian Bureau of Statistics, 2008).

### 2.3. Statistical analysis

Logistic regression was used to examine, separately for men and women, the association between the frequency of cannabis use and meeting the criteria for metabolic syndrome and each of the five individual components. All covariates used in our previous work were included in the adjusted analysis: age, socioeconomic status, diagnosis, smoking status, alcohol use, level of physical activity, cognition, and antipsychotic medication use (Waterreus et al., 2016). Sample weights were used to correct for differential selection probabilities. The number of participants with at least one missing covariate was low: 20 men and 14 women. These were excluded from adjusted analyses which were conducted with SPSS (version 24) and Stata /IC (version 15.1).

## 3. Results

The characteristics of the 735 women and 1078 men are summarized in Table 1. Men were more likely to be using cannabis, tobacco, alcohol and antipsychotic medication and have a diagnosis of schizophrenia. Women were on average slightly older than men and more likely to be in the highest tercile for cognitive function. The proportion of participants who did not provide a fasting blood sample (and so for whom metabolic syndrome could not be determined) did not differ across the three cannabis groups, nor did the proportion of participants

**Table 1**
Characteristics of the SHIP participants by sex.

| | Men *N = 1078* | Women *N = 735* | P value |
|---|---|---|---|
| Age (years), mean (SD) | 37.4 (10.9) | 39.7 (11.4) | < 0.001 |
| Socioeconomic disadvantage, mean (SD) | 979.8 (70) | 979.5 (71) | 0.94 |
| Diagnosis, % | | | < 0.001 |
| schizophrenia | 56.0 | 33.3 | |
| schizoaffective disorder | 14.6 | 18.4 | |
| bipolar, mania | 13.1 | 24.1 | |
| depressive psychosis | 3.1 | 6.5 | |
| delusional disorders & other non-organic psychosis | 5.9 | 3.5 | |
| other* | 7.3 | 14.1 | |
| Cognitive function, % | | | < 0.001 |
| lowest tercile | 32.2 | 24.5 | |
| middle tercile | 28.6 | 26.5 | |
| highest tercile | 26.9 | 39.7 | |
| did not do task | 12.3 | 9.3 | |
| Cannabis use past-year, % | | | < 0.001 |
| non-user | 61.1 | 75.6 | |
| occasional | 15.4 | 11.2 | |
| frequent | 23.5 | 13.2 | |
| Age first used cannabis, mean (SD) | 16.3 (4.7) | 17.1 (5.5) | 0.004 |
| Antipsychotic use, % | | | < 0.001 |
| no | 15.6 | 22.4 | |
| yes but not clozapine | 64.7 | 66.1 | |
| yes clozapine | 19.7 | 11.4 | |
| Current smoker, % | 71.3 | 58.9 | < 0.001 |
| Hazardous alcohol use, % | 48.5 | 38.4 | < 0.001 |
| Physical activity, % | | | 0.03 |
| low | 45.7 | 49.0 | |
| moderate | 36.5 | 38.5 | |
| high | 16.3 | 11.3 | |
| not known | 1.4 | 1.2 | |
| Metabolic syndrome, % | | | 0.97 |
| no | 31.4 | 31.2 | |
| yes | 42.7 | 43.3 | |
| insufficient measures | 26.0 | 25.6 | |
| Meeting threshold for individual criteria[a] | | | |
| Waist circumference, % (n) | 76.4 (805) | 91.3 (639) | < 0.001 |
| Blood pressure, % (n) | 55.0 (581) | 49.3 (347) | 0.02 |
| HDL, % (n) | 55.7 (440) | 58.8 (316) | 0.26 |
| Triglycerides, % (n) | 56.2 (447) | 49.5 (268) | 0.02 |
| Glucose, % (n) | 34.6 (273) | 31.0 (165) | 0.17 |

HDL = high density lipoproteain.
* Other = screen-positive for psychosis but did not meet full criteria for ICD-10 psychosis.
[a] = includes only people who had measurement taken.

with at least one missing covariate.

### 3.1. Cannabis

In the past year, 419 (38.9%) men and 179 (24.4%) women had used cannabis but, although the rate of past-year cannabis use was lower for women, within the group of users, frequency of use was similar for both sexes: 60.4% of men and 54.2% of women were using cannabis on a frequent basis. The mean age of first cannabis use was also similar for both sexes: males 16.3 years and females 17.1 years (see Table 1).

### 3.2. Metabolic syndrome

A total of 798 (74.0%) men and 547 (74.4%) women had sufficient information to determine whether they met the criteria for metabolic syndrome. The prevalence of metabolic syndrome was 57.6% in men and 58.1% in women. Unadjusted bivariate analysis showed the odds of metabolic syndrome decreased with increasing frequency of cannabis use in both sexes (Table 2). When adjusted analyses were run, both occasional and frequent cannabis use in men remained associated with significantly lower odds of metabolic syndrome compared to non-use (AOR = 0.58, 95% CI 0.34-0.99 occasional, AOR = 0.49, 95% CI 0.31-0.80 frequent). However, there was no longer a significant reduction in odds of metabolic syndrome for frequent cannabis-using women. The unadjusted and adjusted odds ratios for the association of cannabis use and all other covariates with metabolic syndrome in men and women with a psychotic illness are provided in the Supplementary table.

### 3.3. Individual metabolic components

Abdominal obesity was the criterion most commonly met by both sexes, with 91.3% of women and 76.4% of men meeting the threshold for elevated waist circumference. There were sex differences with the blood pressure and triglyceride components, with a greater proportion of men than women meeting the threshold criteria (see Table 1). When the mean results for each of the five components were compared across the three cannabis groups for each sex, male frequent cannabis users showed a better cardiometabolic profile than non-users for each of the individual metabolic syndrome components (Table 3). In particular, the mean waist circumference of frequent cannabis users was 10.2 cm smaller than that of non-users. In adjusted analyses, the odds of meeting the threshold for abdominal obesity, hypertension, and elevated triglycerides were all significantly reduced in male frequent cannabis users relative to non-users (Table 2). Lower, but non-significant, odds ratios were also observed for HDL and glucose.

A similar analysis of data for women showed frequent cannabis users had, on average, smaller waist circumferences and a lower fasting plasma glucose than non-users. No differences in the other cardiometabolic measures were seen across cannabis groups. The adjusted odds ratios for meeting the threshold for each of the five metabolic components were not significantly different across the cannabis groups for women, although there was a trend toward lower odds in frequent users relative to non-users in all components.

## 4. Discussion

This is the first study we are aware of to examine the relationship between the frequency of past-year cannabis use and metabolic syndrome separately in men and women with a psychotic disorder. Our data suggest that men who use cannabis (of any frequency) are less likely than non-users to meet the threshold for metabolic syndrome, even after adjusting for a range of potential confounders, including lifestyle factors, cognitive function, and antipsychotic medication use. This was not the case for women. Sex differences were also seen in the relationship between the frequency of cannabis use and the components of metabolic syndrome, most noticeably waist circumference. Only male frequent cannabis users were less likely to meet the threshold for abdominal obesity than non-users, although frequent cannabis use by both sexes was associated with a smaller average waist circumference compared to non-users. Our finding of a better metabolic profile in cannabis users seems counterintuitive since it is well known that cannabis use stimulates the appetite for sweet and high-fat content food. None the less, our findings support previous reports of lower prevalence of obesity associated with cannabis use (Bruins et al., 2016; Hayatbakhsh et al., 2010; Le Strat and Le Foll, 2011; Lieburg et al., 2016; Ngueta et al., 2015; Penner et al., 2013; Rajavashisth et al., 2012; Scheffler et al., 2018; Vidot et al., 2016) and point to complex underlying mechanisms.

Regular use of cannabis may disrupt the complex signaling pathways of the endocannabinoid system (Ceccarini et al., 2015; D'Souza et al., 2008; Hirvonen et al., 2011; Lichtman and Martin, 2005), which plays a role in regulating metabolism and appetite (Pagotto et al., 2006). The main psychoactive component in cannabis, delta-9-tetrahydrocannabinol (THC), has been shown to bind to cannabinoid receptors ($CB_1$ and $CB_2$), and to act as a receptor partial agonist as well as an antagonist (Pertwee, 2008). Of particular relevance is the research showing that blocking receptors with a $CB_1$ receptor antagonist, such as

**Table 2**
Association between cannabis use and metabolic syndrome and its individual components, in men and women with a psychotic illness. Odds ratios* (unadjusted (OR) and adjusted (AOR)) and 95% confidence intervals (CI).

| | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | OR | 95% CI | AOR | 95% CI | N | OR | 95% CI | AOR | 95% CI |
| Metabolic syndrome | | | | | | | | | | |
| non-user | 499 | ref | | ref | | 415 | ref | | ref | |
| occasional | 117 | **0.58** | **0.37-0.89** | **0.58** | **0.34-0.99** | 59 | 0.76 | 0.42-1.36 | 1.15 | 0.56-2.32 |
| frequent | 182 | **0.42** | **0.29-0.61** | **0.49** | **0.31-0.80** | 73 | **0.54** | **0.32-0.92** | 0.68 | 0.37-1.24 |
| Abdominal obesity | | | | | | | | | | |
| non-user | 640 | ref | | ref | | 526 | ref | | ref | |
| occasional | 164 | 0.77 | 0.49-1.20 | 1.04 | 0.62-1.72 | 79 | 0.70 | 0.28-1.74 | 1.14 | 0.45-2.89 |
| frequent | 249 | **0.29** | **0.21-0.41** | **0.42** | **0.28-0.62** | 95 | 0.58 | 0.29-1.15 | 0.95 | 0.39-2.31 |
| Hypertension | | | | | | | | | | |
| non-user | 646 | ref | | ref | | 530 | ref | | ref | |
| occasional | 164 | 0.71 | 0.49-1.02 | 0.82 | 0.54-1.24 | 80 | 0.66 | 0.40-1.10 | 0.85 | 0.47-1.54 |
| frequent | 247 | **0.52** | **0.38-0.71** | **0.66** | **0.46-0.95** | 94 | 0.62 | 0.39-1.00 | 0.65 | 0.36-1.16 |
| HDL | | | | | | | | | | |
| non-user | 493 | ref | | ref | | 405 | ref | | ref | |
| occasional | 114 | 0.87 | 0.56-1.34 | 0.88 | 0.53-1.47 | 59 | 1.10 | 0.60-2.01 | 1.17 | 0.57-2.41 |
| frequent | 183 | **0.60** | **0.42-0.86** | 0.65 | 0.42-1.00 | 73 | 0.95 | 0.55-1.63 | 0.96 | 0.50-1.82 |
| Triglycerides | | | | | | | | | | |
| non-user | 495 | ref | | ref | | 409 | ref | | ref | |
| occasional | 117 | 0.81 | 0.52-1.24 | 0.76 | 0.46-1.25 | 59 | 0.58 | 0.31-1.06 | 0.79 | 0.38-1.68 |
| frequent | 183 | **0.55** | **0.38-0.79** | **0.57** | **0.37-0.89** | 73 | 0.65 | 0.37-1.14 | 0.92 | 0.48-1.75 |
| Glucose | | | | | | | | | | |
| non-user | 486 | ref | | ref | | 404 | ref | | ref | |
| occasional | 119 | **0.51** | **0.31-0.84** | **0.54** | **0.30-0.96** | 58 | 0.74 | 0.38-1.42 | 1.03 | 0.44-2.39 |
| frequent | 183 | **0.67** | **0.45-0.99** | 0.82 | 0.51-1.34 | 70 | **0.33** | **0.15-0.72** | 0.51 | 0.22-2.21 |

Bold values correspond to odds ratios that are statistically significant ($P < 0.05$).

* Weighted to account for differential sampling probabilities and adjusted for age, SES, smoking, alcohol, cognition, diagnosis, physical activity, antipsychotic medication.

**Table 3**
Components of metabolic syndrome across cannabis groups, for men and women with a psychotic illness. Means* and standard deviations (sd).

| | Waist (cm) | Systolic BP (mmHg) | Diastolic BP (mmHg) | HDL (mmol/l) | Triglycerides (mmol/l) | Glucose (mmol/l) |
|---|---|---|---|---|---|---|
| | mean (sd) | mean (sd) | mean (sd) | mean (sd) | mean (sd) | mean (sd) |
| **Men** | | | | | | |
| non-user | 110.4 (17.5) | 126.2 (16.6) | 84.3 (11.3) | 1.1 (0.3) | 2.2 (1.5) | 5.6 (1.2) |
| occasional | 105.6 (18.0) | 125.6 (17.4) | 83.7 (11.6) | 1.1 (0.6) | 2.4 (2.0) | 5.3 (1.0) |
| frequent | 100.2 (17.8) | 122.2 (14.5) | 80.6 (11.2) | 1.2 (0.5) | 1.9 (1.4) | 5.4 (1.1) |
| **Women** | | | | | | |
| non-user | 107.0 (20.2) | 119.3 (16.9) | 83.2 (11.7) | 1.3 (0.4) | 1.8 (1.1) | 5.4 (1.2) |
| occasional | 99.7 (18.3) | 116.6 (15.6) | 82.1 (13.7) | 1.3 (0.6) | 1.6 (1.0) | 5.2 (1.3) |
| frequent | 99.9 (16.7) | 120.2 (17.2) | 82.8 (14.2) | 1.3 (0.3) | 1.7 (0.9) | 5.0 (0.9) |

* Weighted to account for differential sampling probabilities.

rimonabant, resulted in a loss of body weight and body fat, and an improvement in glycaemic and lipid profile (Gelfand and Cannon, 2006; Pi-Sunyer et al., 2006; Van Gaal et al., 2005). Alternatively, other cannabinoids identified in cannabis including cannabidiol or tetrahydrocannabivarin, alone or in combination, may have therapeutic metabolic effects, as has been shown in vivo (Maccarrone et al., 2017; Russo and Guy, 2006; Wargent et al., 2013; Weiss et al., 2006). This does not, however, explain our lack of findings in female cannabis users.

Documented evidence from animal studies suggests that gonadal hormones are involved in the cannabinoid regulation of energy balance (Borgquist et al., 2014; Brown and Clegg, 2010; Riebe et al., 2010; Wagner, 2016) and may also influence cannabinoid receptor density and distribution in a sex-dependent manner (Antinori and Fattore, 2017; Cooper and Craft, 2018). If the sensitivity of the CB receptors to exogenous cannabinoids are differentially modulated by testosterone and estrogen, this may explain the sex differences we observed. Existing literature highlights differences in male and female sensitivity to a number of cannabis-induced effects including hyperphagia, pain relief and dizziness (Cooper and Craft, 2018; Cooper and Haney, 2016; Craft et al., 2013; Diaz et al., 2009). Therefore, it is possible that men are more sensitive than women to the cardiometabolic effects of cannabis, which may explain the greater differences we saw in the cannabis-using men.

The possible role of leptin, an adipocyte-secreted hormone which is associated with a reduced appetite and is regulated by the endocannabinoid system, should also be considered (Zhang et al., 1994). A disruption to the endocannabinoid system by cannabis may affect leptin. Previous investigations into the effects of cannabis on leptin have produced conflicting results but, as pointed out by Moreira et al., (2018), none of these studies examined their data by sex. Their analysis, stratified by sex, found lower leptin levels in male but not female cannabis users compared to non-users. Finally, there has been growing interest in the role played by gut microbiota in health and disease, including cardiovascular diseases and metabolism (Cani et al., 2014; Tang et al., 2017). New evidence suggests that THC may exert an effect on gut microbiota which prevents weight gain (Cluny et al., 2015).

### 4.1. Strengths and limitations

The strength of our study lies in its sampling design. The large representative sample of women (who are often under-represented in cannabis studies), as well as men, ensure 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 our physical health assessments were well calibrated as they did not rely on self-reported or retrospective measures. Although we were able to adjust for a broad range of potential influencing factors, we were unable to take into account, the amount and the potency of cannabis used. Due to the lack of data on the daily amount of cannabis used, we were unable to examine the possibility that the sex differences we observed may be due to men consuming cannabis in greater amounts than females. Furthermore, although we had a large sample of women cannabis users, we may have lacked statistical power to show any differences across the three female cannabis groups. Finally, since this is a cross-sectional study, longitudinal data are needed to establish causality in the association we found.

Our data indicate that, for men only, cannabis use may have cardiometabolic protective effects, which highlights the importance of looking at cannabis use in men and women separately. The challenge now is two-fold: i) to understand the precise role cannabis plays in modulating metabolism in men and why the effect is apparently less in women, and ii) to translate these findings into clinical practice to improve the health of people with a psychotic illness. Finally, we note that, although cannabis may appear to represent a possible new pharmacological treatment for cardiometabolic diseases for men, its negative association with psychosis onset and relapse should not be dismissed(Gage et al., 2016; Schoeler et al., 2016).

## Role of funding source

The SHIP study was funded by the Australian Government Department of Health and Ageing.

## Contributors

VM and AW contributed to the design and implementation of the SHIP study. For this sub study PD and AW conducted the statistical analyses. All authors were involved in the interpretation of results, writing of the manuscript and approved the final version of the manuscript.

## Conflict of interest

No conflict declared

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.11.006.

## References

Alberti, K.G.M.M., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.-C., James, W.P.T., Loria, C.M., Smith, S.C., 2009. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120, 1640–1645.

Antinori, S., Fattore, L., 2017. How CB1 receptor activity and distribution contribute to make the male and female brain different toward cannabinoid-induced effects. In: Melis, M. (Ed.), Endocannabinoids and Lipid Mediators in Brain Functions. Springer, Cham, pp. 27–51.

Australian Bureau of Statistics, 2008. Socio-Economic Indexes for Areas (SEIFA) -Technical Paper. Catalogue number 2039.0.55.001. Australian Bureau of Statistics, Canberra, Australia. http://www.abs.gov.au/ausstats/abs@.nsf/mf/2039.0.55.001/.

Borgquist, A., Meza, C., Wagner, E.J., 2014. The role of AMP-activated protein kinase in the androgenic potentiation of cannabinoid-induced changes in energy homeostasis. Am. J. Physiol. Endocrinol. Metab. 308, E482–E495.

Brown, L., Clegg, D., 2010. Central effects of estradiol in the regulation of food intake, body weight, and adiposity. J. Steroid Biochem. Mol. Biol. 122, 65–73.

Bruins, J., Pijnenborg, M.G., Bartels-Velthuis, A.A., Visser, E., van den Heuvel, E.R., Bruggeman, R., Jörg, F., 2016. Cannabis use in people with severe mental illness: the association with physical and mental health–a cohort study. A pharmacotherapy monitoring and outcome survey study. J. Psychopharmacol. (Oxford) 30, 354–362.

Bush, K., Kivlahan, D.R., McDonell, M.B., Fihn, S.D., Bradley, K.A., 1998. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Arch. Intern. Med. 158, 1789–1795.

Calakos, K.C., Bhatt, S., Foster, D.W., Cosgrove, K.P., 2017. Mechanisms underlying sex differences in cannabis use. Curr. Addict. Rep. 4, 439–453.

Cani, P.D., Geurts, L., Matamoros, S., Plovier, H., Duparc, T., 2014. Glucose metabolism: focus on gut microbiota, the endocannabinoid system and beyond. Diabetes Metab. 40, 246–257.

Castle, D., Jablensky, A., McGrath, J., Carr, V., Morgan, V., Waterreus, A., Valuri, G., Stain, H., McGuffin, P., Farmer, A., 2006. The diagnostic interview for psychoses (DIP): development, reliability and applications. Psychol. Med. (Paris) 36, 69–80.

Ceccarini, J., Kuepper, R., Kemels, D., van Os, J., Henquet, C., Van Laere, K., 2015. [18F] MK-9470 PET measurement of cannabinoid CB1 receptor availability in chronic cannabis users. Addict. Biol. 20, 357–367.

Cluny, N.L., Keenan, C.M., Reimer, R.A., Le Foll, B., Sharkey, K.A., 2015. Prevention of diet-induced obesity effects on body weight and gut microbiota in mice treated chronically with Δ9-tetrahydrocannabinol. PLoS One 10, e0144270.

Cooper, Z.D., Craft, R.M., 2018. Sex-dependent effects of cannabis and cannabinoids: a translational perspective. Neuropsychopharmacology 43, 34.

Cooper, Z.D., Haney, M., 2016. Sex-dependent effects of cannabis-induced analgesia. Drug Alcohol Depend. 167, 112–120.

Craft, R.M., Marusich, J.A., Wiley, J.L., 2013. Sex differences in cannabinoid pharmacology: a reflection of differences in the endocannabinoid system? Life Sci. 92, 476–481.

Craig, C.L., Marshall, A.L., Sjostrom, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Kelund, U., Agneta, Y., Sallis, J.F., Oja, P., 2003. International physical activity questionnaire: 12-Country reliability and validity. Med. Sci. Sports Exerc. 35, 1381–1395.

D'Souza, D.C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., Perry, E., Krystal, J., 2008. Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacology 33, 2505–2516.

Diaz, S., Farhang, B., Hoien, J., Stahlman, M., Adatia, N., Cox, J.M., Wagner, E.J., 2009. Sex differences in the cannabinoid modulation of appetite, body temperature and neurotransmission at POMC synapses. Neuroendocrinology 89, 424–440.

Fattore, L., Fratta, W., 2010. How important are sex differences in cannabinoid action? Br. J. Pharmacol. 160, 544–548.

Gage, S.H., Hickman, M., Zammit, S., 2016. Association between cannabis and psychosis: epidemiologic evidence. Biol. Psychiatry 79, 549–556.

Gelfand, E.V., Cannon, C.P., 2006. Rimonabant: a cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. J. Am. Coll. Cardiol. 47, 1919–1926.

Green, B.O.B., Young, R., Kavanagh, D., 2005. Cannabis use and misuse prevalence among people with psychosis. Br. J. Psychiatry 187, 306–313.

Hayatbakhsh, M.R., O'Callaghan, M.J., Mamun, A.A., Williams, G.M., Clavarino, A., Najman, J.M., 2010. Cannabis use and obesity and young adults. Am. J. Drug Alcohol Abuse 36, 350–356.

Hirvonen, J., Goodwin, R., Li, C.-T., Terry, G., Zoghbi, S., Morse, C., Pike, V., Volkow, N., Huestis, M., Innis, R., 2011. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. Mol. Psychiatry 17, 642–649.

Jablensky, A., McGrath, J., Herrman, H., Castle, D., Gureje, O., Evans, M., Carr, V., Morgan, V., Korten, A., Harvey, C., 2000. Psychotic disorders in urban areas: an overview of the study on low prevalence disorders. Aust. N. Z. J. Psychiatry 34, 221–236.

Ketcherside, A., Baine, J., Filbey, F., 2016. Sex effects of marijuana on brain structure and function. Curr. Addict. Rep. 3, 323–331.

Le Strat, Y., Le Foll, B., 2011. Obesity and cannabis use: results from 2 representative national surveys. Am. J. Epidemiol. 174, 929–933.

Lichtman, A., Martin, B., 2005. Cannabinoid tolerance and dependence. In: Pertwee, R. (Ed.), Cannabinoids. Handbook of Experimental Pharmacology. Springer, Berlin, Heidelberg, pp. 691–717.

Liemburg, E.J., Bruins, J., van Beveren, N., Islam, M.A., Alizadeh, B.Z., Bruggeman, R., Wiersma, D., Cahn, W., Kahn, R., de Haan, L., 2016. Cannabis and a lower BMI in psychosis: what is the role of AKT1? Schizophr. Res. 176, 95–99.

Maccarrone, M., Maldonado, R., Casas, M., Henze, T., Centonze, D., 2017. Cannabinoids therapeutic use: what is our current understanding following the introduction of THC, THC: CBD oromucosal spray and others? Expert. Rev. Clin. Pharmacol. Drug Ther. 10, 443–455.

McGuffin, P., Farmer, A., Harvey, I., 1991. A polydiagnostic application of operational criteria in studies of psychotic illness: development and reliability of the OPCRIT system. Arch. Gen. Psychiatry 48, 764–770.

Moreira, F.P., Wiener, C.D., Oliveira, J.Fd., Souza, L.D., da Silva, R.A., Portela, L.V., Lara,

D.R., Jansen, K., Oses, J.P., 2018. Gender differences of cannabis smoking on serum leptin levels: population-based study. Rev. Bras. Psiquiatr. 40, 216–219.
Morgan, V.A., McGrath, J.J., Jablensky, A., Badcock, J.C., Waterreus, A., Bush, R., Carr, V., Castle, D., Cohen, M., Galletly, C., Harvey, C., Hocking, B., McGorry, P., Neil, A.L., Saw, S., Shah, S., Stain, H.J., Mackinnon, A., 2014. Psychosis prevalence and physical, metabolic and cognitive co-morbidity: data from the second Australian national survey of psychosis. Psychol. Med. (Paris) 44, 2163–2176.
Morgan, V.A., Waterreus, A., Jablensky, A., Mackinnon, A., McGrath, J.J., Carr, V., Bush, R., Castle, D., Cohen, M., Harvey, C., 2012. People living with psychotic illness in 2010: the second Australian National Survey of Psychosis. Aust. N. Z. J. Psychiatry 46, 735–752.
Ngueta, G., Bélanger, R.E., Laouan-Sidi, E.A., Lucas, M., 2015. Cannabis use in relation to obesity and insulin resistance in the Inuit population. Obesity 23, 290–295.
Pagotto, U., Marsicano, G., Cota, D., Lutz, B., Pasquali, R., 2006. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr. Rev. 27, 73–100.
Penner, E.A., Buettner, H., Mittleman, M.A., 2013. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am. J. Med. 126, 583–589.
Pertwee, R.G., 2008. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. Br. J. Pharmacol. 153, 199–215.
Pi-Sunyer, F.X., Aronne, L.J., Heshmati, H.M., Devin, J., Rosenstock, J., Group, R.-N.A.S., 2006. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 295, 761–775.
Rajavashisth, T.B., Shaheen, M., Norris, K.C., Pan, D., Sinha, S.K., Ortega, J., Friedman, T.C., 2012. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. BMJ Open 2, e000494.
Randolph, C., Tierney, M.C., Mohr, E., Chase, T.N., 1998. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J. Clin. Exp. Neuropsychol. 20, 310–319.
Riebe, C.J., Hill, M.N., Lee, T.T., Hillard, C.J., Gorzalka, B.B., 2010. Estrogenic regulation of limbic cannabinoid receptor binding. Psychoneuroendocrinology 35, 1265–1269.
Russo, E., Guy, G.W., 2006. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med. Hypotheses 66, 234–246.
Saunders, J.B., Aasland, O.G., Babor, T.F., de la Fuente, J.R., Grant, M., 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction 88, 791–804.
Scheffler, F., Kilian, S., Chiliza, B., Asmal, L., Phahladira, L., du Plessis, S., Kidd, M., Murray, R., Di Forti, M., Seedat, S., 2018. Effects of cannabis use on body mass, fasting glucose and lipids during the first 12 months of treatment in schizophrenia spectrum disorders. Schizophr. Res. 199, 90–95. https://doi.org/10.1016/j.schres.2018.02.050.
Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Ajnakina, O., Gayer-Anderson, C., Colizzi, M., Quattrone, D., Behlke, I., 2016. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. Lancet Psychiatry 3, 947–953.
Tang, W.W., Kitai, T., Hazen, S.L., 2017. Gut microbiota in cardiovascular health and disease. Circ. Res. 120, 1183–1196.
Thompson, C.A., Hay, J.W., 2015. Estimating the association between metabolic risk factors and marijuana use in US adults using data from the continuous National Health and Nutrition Examination Survey. Ann. Epidemiol. 25, 486–491.
United Nations Office on Drugs and Crime, 2015. World Drug Report 2015. . https://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf.
Van Gaal, L.F., Rissanen, A.M., Scheen, A.J., Ziegler, O., Rössner, S., 2005. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 365, 1389–1397.
Vidot, D.C., Prado, G., Hlaing, W.M., Florez, H.J., Arheart, K.L., Messiah, S.E., 2016. Metabolic syndrome among marijuana users in the United States: an analysis of National Health and Nutrition Examination Survey data. Am. J. Med. 129, 173–179.
Wagner, E.J., 2016. Sex differences in cannabinoid-regulated biology: a focus on energy homeostasis. Front. Neuroendocrinol. 40, 101–109.
Wargent, E.T., Zaibi, M.S., Silvestri, C., Hislop, D.C., Stocker, C.J., Stott, C.G., Guy, G.W., Duncan, M., Di Marzo, V., Cawthorne, M.A., 2013. The cannabinoid [Delta]9-tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity. Nutr. Diabetes 3, e68.
Waterreus, A., Di Prinzio, P., Watts, G., Castle, D., Galletly, C., Morgan, V., 2016. Metabolic syndrome in people with a psychotic illness: is cannabis protective? Psychol. Med. 46, 1651–1662.
Waterreus, A., Morgan, V.A., Castle, D., Galletly, C., Jablensky, A., Di Prinzio, P., Shah, S., 2012. Medication for psychosis - consumption and consequences: the second Australian national survey of psychosis. Aust. N. Z. J. Psychiatry 46, 762–773.
Weiss, L., Zeira, M., Reich, S., Har-Noy, M., Mechoulam, R., Slavin, S., Gallily, R., 2006. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. Autoimmunity 39, 143–151.
Wetherington, C.L., 2007. Sex-gender differences in drug abuse: a shift in the burden of proof? Exp. Clin. Psychopharmacol. 15, 411.
Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, J.M., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372, 425.