Cumulative Cardiovascular Disease Risk and Triglycerides Differentially Relate to Subdomains of Executive Function in Bipolar Disorder.

Running title: CVD risk factors and executive function in BD

Tamsyn E. Van Rheenen*, Roger S. McIntyre, Vicent Balanzá-Martínez, Michael Berk, Susan L. Rossell

1Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Melbourne, Australia
2Centre for Mental Health, Faculty of Health, Arts and Design, School of Health Sciences, Swinburne University, Melbourne, Australia
3Department of Psychiatry, St Vincent’s Hospital, VIC, Australia
4Teaching unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, CIBERSAM, Valencia, Spain
5Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain
6The Institute for Mental and Physical Health and Clinical Translation, Deakin University, Geelong, Australia
7Barwon Health, PO Box 281, Geelong, Victoria, 3220, Australia
8Orygen, The National Centre of Excellence in Youth Mental Health, the Department of Psychiatry, and the Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Australia
9Mood Disorders Psychopharmacology Unit, Brain and Cognition Discovery Foundation University of Toronto, Toronto, Canada.

* Corresponding author current postal address:
Dr Tamsyn Van Rheenen
Melbourne Neuropsychiatry Centre, Level 3, Alan Gilbert Building, 161 Barry St, Carlton, Vic 3053, Australia, tamsyn.van@unimelb.edu.au
Abstract

Objectives: Cardiovascular disease is disproportionately prevalent in bipolar disorder (BD) and has been linked to cognition in preliminary studies. Herein we evaluate the association between known risk factors for cardiovascular disease and executive function in BD patients compared to healthy controls.

Methods: In a sample of n=57 individuals (n=23 BD, n=34 controls) we assessed two subdomains of executive function; cognitive flexibility (using the Trail Making Test - Part B) and cognitive inhibition (using the Stroop Colour Word Interference Task). Cardiovascular risk was assessed by means of serum triglyceride levels, body mass index (BMI) and waist circumference, as well as dietary saturated fat intake and a sex-specific cumulative cardiovascular risk score calculated using the Framingham Heart Study method.

Results: Patients with BD had higher BMI and waist circumference, with more BD patients categorized as having central obesity than controls. In the BD group only, higher triglyceride levels were associated with worse cognitive flexibility, and elevated cumulative cardiovascular disease risk was associated with worse cognitive inhibition. No correlations between cardiovascular risk factors and executive function were evident in the control group.

Limitations: The study was limited by the small sample size and should be considered hypothesis-generating

Conclusions: The associations between triglyceride levels, cumulative cardiovascular disease risk and executive functioning evident in BD in this study preliminarily indicate the potential for mechanistic overlap of physical health and cognitive function in the disorder.

Keywords: metabolic syndrome, obesity, diet, BMI, lipids, Framingham Heart Risk Score, cognition, cognitive flexibility, cognitive inhibition, depression, psychiatry, mental health, neuropsychology, heart
Introduction.

It is well-recognized that individuals with bipolar disorder (BD) are at an increased risk of cardiovascular disease (CVD) (Goldstein, 2017). Indeed, medical morbidity rates in BD are elevated relative to the general population, by virtue of a heightened prevalence of diabetes, obesity, dyslipidaemia, hypertension and a clustering of these CVD risk factors called the metabolic syndrome (Goldstein, 2017; Goldstein et al., 2009a; McIntyre et al., 2010). Not only do CVD risk factors contribute to increased mortality, but they may predispose to adverse brain health via vascular and/or immune and metabolic pathways. For example, available evidence in BD patients and those at-risk for the disorder, indicates that the anatomical structure of the brain is affected by body mass, with reductions in brain volume, thickness and white matter microstructure reported in overweight/obese individuals compared to those of normal weight (Bora et al., 2019; Kuswanto et al., 2014; Mansur et al., 2018).

It is previously documented that CVD risk factors associate particularly consistently with frontal lobe systems and the cognitive domain of executive function (Nishtala et al., 2014; Oveisgharan and Hachinski, 2010; Rostamian et al., 2015; Wiberg et al., 2010; Wolfe et al., 1990). This is thought to relate to an association of CVD-risk and white matter lesions in cortico-subcortical neural circuits that mediate executive processes rather than other neural circuitry, such as the medial temporal lobe, which governs memory (Prins et al., 2005; Pugh and Lipsitz, 2002; Rostamian et al., 2015; Tullberg et al., 2004). Relevantly, executive dysfunction in BD has been linked to deep white matter hypointensities (Rolstad et al., 2016), and while there is substantial evidence of cognitive impairment in BD across a range of domains, executive function is of key interest given meta-analytic evidence of large case-control effects and its relevance as an endophenotype (Balanzá-Martínez et al., 2008; Miskowiak et al., 2017; Van
Rheenen et al., 2017; Van Rheenen and Rossell, 2014a). More pertinently, despite the sparse longitudinal cognitive literature in BD generally suggesting that the cognitive trajectory is set early on and remains stable across time (Van Rheenen et al., 2019), there is some preliminary longitudinal data suggesting that executive impairments specifically, may decline as a function of illness duration (Torrent et al., 2012). This raises the possibility that, in comparison to other cognitive domains, impairment in executive function in BD is more closely linked to CVD risk and morbidity; which is itself known to increase with age and has been associated with a more severe BD disease course (Calkin et al., 2015; Fiedorowicz et al., 2009; Rizzo et al., 2014).

The majority of studies in the burgeoning literature examining associations between CVD risk factors and cognitive function in BD have examined Body Mass Index (BMI) or the presence of obesity, defined categorically (Bora et al., 2019). A recent BD meta-analysis indicated that the most robust association between obesity/overweight and cognitive dysfunction was for the executive domain of cognition, consistent with prior work documenting a CVD risk-executive function association (Bora et al., 2019). To date, few BD studies of cognition have explicitly examined central obesity - indexed by waist circumference or waist-hip-ratio. There is evidence that central adiposity more strongly predicts health risk and mortality than BMI, and it therefore may have more relevance to cognitive function (Janssen et al., 2004; Staiano et al., 2012). Associations between waist circumference and increased impulsivity (Naiberg et al., 2016a), and between waist-hip-ratio and cognitive inhibition, immediate, and delayed verbal memory (Lackner et al., 2016), have been reported in preliminary BD studies. Worse executive function has also been found in BD patients with comorbid metabolic syndrome (Bai et al., 2016), with three studies showing associations between cognition and individual metabolic syndrome components (Hubenak et al., 2015; Hui et al., 2019; Naiberg et al., 2016a). In these
studies, negative associations between high density lipoprotein (HDL) and language and memory (Hui et al., 2019), hypertension and global cognition (Hubenak et al., 2015) and triglycerides and executive function were reported (Naiberg et al., 2016a).

Identifying factors that may influence and/or be influenced by cognition in BD is relevant insofar as cognitive function is a critical mediator of psychosocial function (Mora et al., 2013; Solé et al., 2012; Van Rheenen and Rossell, 2014b). Available studies have generally not evaluated central-adiposity or dyslipidaemia with respect to cognitive performance in BD, nor the impact of dietary fat consumption despite its known implications for incident diabetes and mental well-being (Firth et al., 2019; Francis and Stevenson, 2013). Similarly, to our knowledge, no BD studies have examined the extent to which cumulative CVD risk impacts cognition in the disorder using the Framingham Heart Risk Score (FRS; Pencina et al., 2009). This sex-specific multivariable weighted score is elevated in BD and is strongly associated with cognitive decline in the ageing population (Coello et al., 2019; Kaffashian et al., 2013). It has been shown to be a better indicator of CVD events than the convergence of multiple risks factors subsumed within a diagnosis of the metabolic syndrome (Wannamethee et al., 2005).

Herein we aimed to evaluate the association between executive function and a composite risk score calculated using the Framingham Heart Study formula. We further aimed to evaluate the association of executive function and other CVD risk factors including BMI, waist circumference, serum triglycerides and dietary fat intake. Based on previous literature, we hypothesised that CVD risk factors would be higher in the BD group compared to controls, and that these risk factors would be associated with poor executive performance in the BD group.

Methods
All procedures contributing to this work comply with the ethical standards of the Alfred Hospital Human Ethics Review Board and with the Declaration of Helsinki Declaration.

Participants

The clinical sample comprised 23 patients (n=15 female, n=8 male) with DSM-IV-TR BD diagnoses confirmed using the Mini International Neuropsychiatric Interview (MINI: Sheehan et al., 1998). Patients were all out-patients recruited via community support groups and general advertisements. Current mood symptomology was assessed using the Young Mania Rating Scale (YMRS: Young et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery and Asberg, 1979). Ten participants were considered to be affectively stable, as defined by a MADRS score ≤12 and YMRS ≤10. The remainder of the BD sample were symptomatic. Patients with significant visual or verbal impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded.

A control sample of 34 healthy participants (n=20 female, n=14 male) were recruited by general advertisement or pre-existing participant databases. Using the MINI screen, no control participant had a current diagnosis or previous history of psychiatric illness. An immediate family history of mood and psychiatric disorder in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and current psychiatric medication use was exclusion criteria for all controls.

All participants included in this analysis were fluent in English, were between the ages of 20 and 60 years and had an estimated pre-morbid IQ as scored by the Wechsler Test of Adult Reading (WTAR) of >90. No participant included in the analysis had a history of ‘Hard’ CVD (stroke or myocardial infarction).
**Measures**

*Cardiovascular risk factors.*

A composite cardiovascular risk score (FRS) was calculated using the Framingham Heart Study formula (Pencina et al., 2009) (available from https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-30-year-risk/) to quantify 30-year risk for ‘hard’ CVD outcomes (e.g. stroke, myocardial infarction, and coronary death) by accounting for several vulnerability factors at once. The FRS takes into account sex, age, systolic blood pressure, Total Cholesterol (TCH), HDL, smoking status, diabetes history and current treatment for hypertension.

Blood pressure was measured using an OMRON automatic blood pressure monitor while the participant was seated with their arm out, palm upright and legs uncrossed. Three blood pressure readings were obtained. The first reading was discarded and the second and third readings were averaged to determine a final blood pressure score. Blood samples were collected via venepuncture. A lipid level profile was obtained for each person from Hospital Pathology. Blood samples were non-fasting; however, they were collected at the end of the study day after an absence of food consumption for approximately 2-3 hours.

Triglyceride levels, BMI, waist circumference, and consumption of dietary saturated fat are also risk factors for CVD but are not included in the calculation of the FRS. These variables were examined independently. Triglyceride levels were obtained within the lipid panel. Height, weight and waist circumference were obtained using the procedures of the Baker IDI Healthy Hearts Clinic (https://baker.edu.au/). Height was taken using a retractable measuring tape to the nearest 0.5cm. Participants were instructed to remove shoes, stand straight with their back and heels against the wall and look straight ahead. Weight was measured with a digital scale with
shoes, heavy coats, wallets, heavy jewellery, mobile phones removed. Waist measurements were taken at the narrowest circumference between the top of the pelvis and lowest rib. Participants were instructed to breath naturally. BMI was calculated from height and weight measurements using the formula: weight (kg)/height(m)^2.

Dietary fat intake was measured with the MEDFICTS dietary questionnaire (Kris-Etherton et al., 2001), a tool recommended by the National Cholesterol Education Program to assess adherence to the Adult Treatment Panel (ATP) III Therapeutic Lifestyle Changes diet (National Cholesterol Education Program, 2002). The MEDFICTS assesses general food consumption in 8 categories: Meats, Eggs, Dairy, Fried foods, fat In baked goods, Convenience foods, fats added at the Table, and Snacks. Food items within each category are assigned based on total fat content as either desirable or undesirable. Weighted numeric values are then assigned to each food item based on weekly consumption and serving size of food in these categories. A total score is then derived, with higher scores indicating diets with more dietary fat. Specifically, a score of < 40 suggests the diet is low in saturated and total fat (consistent with a step 2 diet), a score 40 - 70 indicates the diet is good but would benefit from reducing saturated fat intake (diet is consistent with a step 1 diet), and a score of Score >70 suggests the diet contains too much saturated and total fat (Taylor et al., 2003).

Cognition.

Executive function was assessed with the Stroop Colour-Word Test (SCWT-I) inhibition contrast score (Stroop, 1935), and the Trails Making Test-Part B (TMT-B) (Reitan, 1958), two widely used measures of cognitive flexibility and inhibition. Note that the Neuropsychological Assessment Battery; Mazes Test was also available in this dataset as a measure of executive
function. However, we chose to focus the analyses on the TMT-B and the SCWT *a-priori*, because these tests are more sensitive to detecting impairment in BD (Yatham et al., 2010) and have been more consistently linked to vascular impairment in CVD and ageing samples (e.g., Cohen et al., 2009; Nishtala et al., 2014; Rostamian et al., 2015). There was also missing data for some participants on the NAB: Mazes, and the small sample size of the study limited a comprehensive cognitive assessment. The SCWT-I requires participants to name the colour of blocks, read colour names and name the ink colour of words denoting a conflicting colour aloud. The dependent variable is time to complete each trial, from which a difference score controlling for the lower order influence of word reading and colour naming on inhibition is calculated. Higher scores represent worse interference control (i.e., worse inhibition of a pre-potent response). The TMT-B requires participants to connect a series of targets in sequential order, alternating between numbers to letters. The dependent variable is time to complete, with higher scores indicating worse cognitive flexibility.

**Statistical Analysis**

All analyses were performed using the Statistical Package for the Social Sciences version 24. Given that the BD sample comprised both symptomatic and affectively stable participants, we conducted preliminary correlational analyses to examine the association between the CVD risk factors or cognitive performance and the MADRS/YMRS scores/those categorically classified as affectively stable or symptomatic. No significant correlations were evident, and thus symptom status/scores were not considered in subsequent analyses. We subsequently assessed group differences in age, sex and premorbid IQ via one-way between-groups Analysis of Variance and Chi Square Tests. The two latter variables did not differ by group, but due to an
observed group difference in age, bivariate and point biserial correlations (where relevant) were conducted to ascertain the association between age and the variables of interest. As age had a significant effect (using a conservative alpha of \( p = .01 \) to account for multiple tests) on FRS (HC and BD) and TMT-B scores (HC only), it was incorporated into subsequent group-comparisons of these variables as either a covariate (FRS) or age*dx interaction term (TMT-B). An interaction term was included as age could not be included as a covariate given differences in age-TMT-B interactions between HCs and BDs, which would violate homogeneity of regression slopes. Age was not controlled in BD-only analyses of TMT-B. In keeping with the methods of Naiberg et al. (2016a), who conducted one of the only previous studies on this topic using several of the variables of interest here, analyses of (co)variance and Chi Square or Fischer’s Exact Tests were used as appropriate, to compare cognitive performance and CVD risk factors between groups. Group differences in CVD risk factors were examined as continuous variables, as well as categorical variables reflecting high and low risk according to standard criteria (see Supplementary Material for details about threshold criteria).

Bivariate or partial correlations (controlling for age, where relevant) were then performed on the continuous measures to examine the association between CVD risk and executive function in BD and healthy controls separately. Fishers r-t-Z transforms were subsequently used to assess for significant between-group differences in the Pearson’s r coefficients of correlations that were significant (after correction) within each group (\( Z \) values \( \geq 1.96 \) are significant at \( p < .05 \) and \( \geq 2.33 \) are significant at \( p < .01 \)). Variables showing significant within group correlations were also included in subsequent within-group linear regression analyses to determine the variance explained in executive functioning scores by relevant CVD risk factors. To account for type I error associated with multiple testing, a False Discovery Rate (FDR) of 5% (i.e., \( p < .05 \)) was first
applied to the analysis of CVD risk/cognition group differences using the Benjamini and Hochberg (1995) method. Further FDR correction was applied separately to correlational analyses in the BD and HC groups. As an indication of robustness, and for ease of interpretation for readers unfamiliar with this correction method, we also report results as per the Bonferroni correction method.

Results

Group comparisons of the demographic and clinical characteristics of the sample are summarized in Table 1. Group comparisons of CVD risk factors and cognitive performance are reported in Table 2. BD patients were significantly older than controls (p=.011) but there were no differences in sex distribution (p=.627), or premorbid IQ (p=.207). Antipsychotics were used by 35% of the BD group, while mood stabilisers were used by 70%.

Numerically, BD participants had worse SCWT-I scores than controls (Cohen’s d=-0.54, p=.041 uncorrected), although this result did not survive FDR correction. Although TMT-B scores did not significantly differ significantly between groups, a moderate-large effect size was also evident favouring better numerical performance in controls (Cohen’s d=-0.73, p=.288 uncorrected). The number of BMI-defined obese participants did not differ according to diagnostic group, but the BD group had significantly (FDR corrected) higher BMI (Cohen’s d=0.84, p=.002 uncorrected) and increased waist circumference (Cohen’s d= 0.81, p=.003 uncorrected) compared to controls. More BD participants than controls were also classified as having central obesity (74% vs. 29%, p=.001 uncorrected, p<.05 FDR corrected). On other categorical variables, there were no significant differences between groups in the proportions of high/low triglycerides, high-mod/low dietary fat and high-moderate/low- 30-year risk for hard
CVD. There were also no significant differences between groups on the continuous FRS, dietary fat intake score or triglyceride levels (d=0.13, d=0.12, d=0.31 respectively).

Correlational analyses (Table 3) revealed a general absence of significant correlations in the control group (Pearson’s r range -.13 – -.36), with the exception of a correlation between dietary fat intake and TMTB (p=.042) that did not survive correction. In the BD group, SCWT-I scores were significantly positively correlated with the FRS (r=.55, p=.005 uncorrected), while TMT-B scores were positively correlated with triglyceride levels (r=.61, p=.002 uncorrected). Both correlations survived FDR multiple comparison correction, and the correlation coefficients differed significantly from controls - being larger (and positive) in the BD patients (z=2.49, respectively z=2.78).

Two subsequent linear regressions were conducted in the BD sample to identify the percentage of variance explained in either the FRS or triglyceride levels as a function of either the SCWT-I or the TMT-B, respectively. Hierarchical regression controlling for age (given its correlation with FRS in the BD group) was conducted in the former, while standard regression was conducted in the latter. These regressions indicated that 29% of the variance in SCWT-I scores was explained by FRS, over and above the effect of age (adjusted r² change =0.29; F(1,20)=5.501, p=.01), while 34.6% of the variance in TMT-B scores were explained by triglyceride levels (adjusted r² change =0.35; F(1,21)=12.65, p=.002). Note that all significant FDR corrected values reported above also survived correction using the more conservative Bonferroni method (refer to Tables 2 and 3 for details).

Discussion
In this study in the BD group only, higher CVD risk using the 30-year FRS was associated with worse cognitive inhibition, while higher triglyceride levels were associated with worse cognitive flexibility. The FRS and triglycerides explained around a third of the variance (29%) in cognitive inhibition and cognitive flexibility (35%) respectively. These correlations are consistent with existing research broadly linking CVD risk factors including BMI/obesity and the presence of metabolic syndrome to cognitive functioning in BD (Bora et al., 2019). However, to our knowledge, this is the first study of BD to examine and report a link between the FRS and cognitive performance, with our findings providing preliminary evidence that elevated clustering of CVD risk factors related to cholesterol levels, blood pressure, diabetes presence and smoking status in BD are associated with a decrement to cognitive inhibition.

Notably, in our data the FRS was not related to cognitive flexibility in BD. In contrast, elevated triglyceride levels – the key dyslipidaemia of the metabolic syndrome and one closely tied to insulin resistance - correlated with reduced cognitive flexibility but not cognitive inhibition in the BD group. This is consistent with a meta-analysis reporting co-occurring impairments in cognitive flexibility but not inhibition in diabetes (Brands et al., 2005). One previous study of BD adolescents also linked impulsivity - a close correspondent of cognitive inhibition - to high blood pressure but not triglyceride level (Naiberg et al., 2016b); the former is captured within the FRS whilst the latter is not. Another study of the same sample linked triglyceride levels but not blood pressure to poor performance on the intra-dimensional extra-dimensional set-shifting task - an alternative measure of the cognitive flexibility sub-domain (Naiberg et al., 2016a). Although highly speculative, in combination these findings raise the possibility that vascular abnormalities (captured within the FRS) are more closely tied to
cognitive inhibition in BD, while *metabolic* abnormalities (e.g. triglyceride levels) are more closely tied to cognitive flexibility.

In this study despite increased BMI and high levels of central obesity in the BD group, no correlations were evident between BMI or waist circumference and executive function in BD patients. While this is inconsistent with some previous work (Lackner et al., 2016; Mora et al., 2017), it is consistent with previous findings in which elevated BMI did not explicitly correlate with cognitive flexibility in BD adolescents while elevated triglycerides did (Naiberg et al., 2016a). Elevated triglyceride levels have been implicated as one mechanism by which obesity might induce cognitive impairment (Farr et al., 2008). Thus, despite the absence of a direct relationship between BMI or waist circumference and executive functioning here, it remains possible that triglyceride levels are an indirect mediator of a BMI-cognitive flexibility effect. Indeed, previous work has shown that metabolic factors mediate the effect of waist circumference on executive performance in healthy adolescents (Bugge et al., 2018).

The mechanisms subserving the association of dyslipidaemia and cognition are not fully understood. Circulating triglycerides readily cross the blood-brain-barrier and control the uptake of insulin, leptin and ghrelin, the key hormone regulators of appetite and obesity (Banks et al., 2018). Triglycerides, insulin resistance and obesity have each been independently found to elevate inflammation and oxidative stress, while cognitive impairment is attenuated by triglyceride lowering medications that themselves lower oxidative stress and inflammation (Cámara-Lemarroy et al., 2015; Farr et al., 2008; Goldstein et al., 2009b; Welty, 2013). Thus, the adverse impact of elevated triglycerides on executive function seen in the current and past work may potentially be explained by the role of triglycerides in regulating immune-relevant processes that are implicated in cognitive dysfunction in BD (Rosenblat et al., 2015; Welty, 2013). An
alternative explanation is that poor executive function might causally influence triglyceride levels by affecting lifestyle choices. However, given the absence of associations in our data between cognitive function and dietary fat consumption, unhealthy dietary choices specifically, may not play a role.

The findings of our study should be interpreted with the following limitations in mind. First, lipid profiles were measured from bloods from which the typical overnight fasting period was not adhered. However, there is mounting evidence that non-fasting lipids are equivalent, if not better predictors of CVD events than fasting lipids (Bansal et al., 2007; Langsted and Nordestgaard, 2019; Nordestgaard et al., 2007). Second, the sample was relatively small, and the healthy controls were younger than the BD patients in this study. While an age-matched sample is certainly the ideal scenario, age was not correlated with most CVD risk factors in this sample; and was appropriately covaried in the statistical analyses concerning the CVD-risk variable for which it was (i.e the FRS). Third, as we did not include a psychiatric control group, it is unclear to what extent the presence or magnitude of observed correlations between CVD risk factors and executive function are specific to BD. Fourth, given the mixed mood states of BD patients, it remains possible that mood state heterogeneity had an effect on the results. However, in our preliminary analysis we did not identify correlations between mood symptom severity scores and the variables of interest. Finally, although second-generation antipsychotics have been linked to increased CVD risk including weight gain, we did not control for them in our analyses given their use in only a small proportion of the BD sample (Newcomer, 2007; Yumru et al., 2007). In light of this, it is unlikely they were driving the increased-BMI/central obesity seen in the BD group; however, we cannot discount that they may have had an effect. Similarly, we did not control for lithium use, although it is possible that this may explain the absence of FRS
differences between groups given that there is some indication that lithium use may protect against factors conferring excess CVD mortality in BD (Ahrens et al., 1995).

Unfortunately, the modest sample size of the current study limited our capacity to more comprehensively model predictors, covariates and examine for mediating effects in the data. Nonetheless, the robust, albeit preliminary, associations between triglycerides, the FRS and executive functioning in BD evident even in a sample of this size highlights the potential relevance of interactions between physical and cognitive health in BD. Since the findings of this study can be considered hypothesis-generating, future studies should not only aim to replicate our findings, but also to examine CVD-risk associations with reward-relevant behaviours of which impairments are evident in BD (Whitton et al., 2015). This deserves attention as such behaviours are mediated by cortico-striatal neural loops that are highly susceptible to vascular insults (Mega and Cummings, 1994; Pugh and Lipsitz, 2002), and as links between reward-related cognition and obesity are evident in closely-related psychiatric populations (Mansur et al., 2019). Further research prospectively analysing temporal associations between CVD risk and executive impairment in BD would also be useful in disentangling cause and effect. Finally, to our knowledge no other studies have examined the link between diet quality and cognition in BD (Van Rheenen et al., 2019), but there is evidence that modifiable risk factors such as diet hold promise for deterring age-related cognitive decline (Middleton and Yaffe, 2009). Thus, further research is needed to assess whether other types of dietary pattern, such as adherence to a Mediterranean diet, may help to manage the cognitive dysfunction associated with BD.
References


National Cholesterol Education Program, 2002. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). National Cholesterol Education Program, National Heart, Lung, and Blood ....


### Table 1. Demographic and clinical characteristics of the sample

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n=34)</th>
<th>Bipolar disorder (n=23)</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Proportion (%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.97</td>
<td>11.92</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>111.58</td>
<td>6.78</td>
<td></td>
</tr>
<tr>
<td>Subtype (bipolar I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis history (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of diagnosis</td>
<td>30.00</td>
<td>10.41</td>
<td></td>
</tr>
<tr>
<td>Age of symptom onset</td>
<td>22.38</td>
<td>12.03</td>
<td></td>
</tr>
<tr>
<td>MADRS</td>
<td>15.13</td>
<td>9.53</td>
<td></td>
</tr>
<tr>
<td>YMRS</td>
<td>6.17</td>
<td>4.40</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: MADRS = Montgomery Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale

*Significant at p<.05

*aWithin-group proportion
Table 2. Cardiovascular disease risk factors and executive functioning in the sample.

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n=34)</th>
<th>Bipolar disorder (n=23)</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Number</td>
</tr>
<tr>
<td><strong>Categorical variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High FRS</td>
<td>6</td>
<td>24.83</td>
<td>17.65</td>
</tr>
<tr>
<td>High circulating triglycerides</td>
<td>6</td>
<td>6</td>
<td>17.6</td>
</tr>
<tr>
<td>Obesity</td>
<td>3</td>
<td>3</td>
<td>8.82</td>
</tr>
<tr>
<td>Central obesity</td>
<td>10</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>Moderate – high dietary saturated fat</td>
<td>18</td>
<td>18</td>
<td>52.94</td>
</tr>
<tr>
<td><strong>Continuous variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.83</td>
<td>4.33</td>
<td>0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>84.15</td>
<td>11.86</td>
<td>95.39</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.48</td>
<td>0.77</td>
<td>1.80</td>
</tr>
<tr>
<td>Dietary saturated fat</td>
<td>42.74</td>
<td>11.92</td>
<td>44.09</td>
</tr>
<tr>
<td>SCWT-I (seconds)</td>
<td>22.74</td>
<td>8.45</td>
<td>28.98</td>
</tr>
<tr>
<td>TMT-Bc (seconds)</td>
<td>55.10</td>
<td>25.00</td>
<td>72.39</td>
</tr>
</tbody>
</table>
Note: FET = Fisher’s Exact Test (no test statistic provided); BMI = body mass index; FRS = Framingham Heart Risk Score; SCWT-I = Stroop Colour Word Task – interference trial; TMTB = Trail Making Test B. Categorical variables reflect high CVD risk according to standard criteria (see Supplementary Material for details about threshold criteria).

a Within-group proportion
b Controlling for age (SDs calculated from SE)
c Controlling for age and age*dx interaction

** p<.05 FDR corrected. Note that significant FDR corrected values also survive the more conservative Bonferroni correction (alpha of .05/12 tests=.004)
Table 3. Correlations between cardiovascular disease risk factors and executive functioning in the BD group and healthy controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cognitive Test</th>
<th>Triglycerides</th>
<th>BMI</th>
<th>Waist Circumference</th>
<th>Dietary saturated fat</th>
<th>FRS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>SCWT-I</td>
<td>0.270</td>
<td>0.113</td>
<td>0.144</td>
<td>-0.047</td>
<td>0.554**</td>
</tr>
<tr>
<td></td>
<td>TMT-B</td>
<td>.613**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td>SCWT-I</td>
<td>-.167</td>
<td></td>
<td>.073</td>
<td>-.160</td>
<td>-.132</td>
</tr>
<tr>
<td></td>
<td>TMT-B*</td>
<td>-.130</td>
<td>-.204</td>
<td>-.361</td>
<td>-.189</td>
<td>-.185</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index; FRS = Framingham Heart Risk Score; SCWT-I = Stroop Colour Word Task – interference trial; TMTB = Trail Making Test B. Note only continuous variables were used in correlational analyses.

*a Controlling for age

**p<.05 FDR corrected. Note that significant FDR corrected values also survive the more conservative Bonferroni correction (alpha of .05/10 correlational tests per group=.005).

Bolded correlation coefficients differ between BD and control groups at p<.01 based on Fischer’s r to z transformation.
Cumulative Cardiovascular Disease Risk and Triglycerides Differentially Relate to Subdomains of Executive Function in Bipolar Disorder; preliminary findings.

Supplementary Material

Tamsyn E. Van Rheenen*1,2, Roger S. McIntyre8, Vicent Balanzá-Martínez4, Michael Berk5,6,7, Susan L. Rossell2,3

1Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Melbourne, Australia
2Centre for Mental Health, Faculty of Health, Arts and Design, School of Health Sciences, Swinburne University, Melbourne, Australia
3Department of Psychiatry, St Vincent’s Hospital, VIC, Australia
4Teaching unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, CIBERSAM, Valencia, Spain
5The Institute for Mental and Physical Health and Clinical Translation, Deakin University, Geelong, Australia
6Barwon Health, PO Box 281, Geelong, Victoria, 3220, Australia

* Corresponding author current postal address:
Dr Tamsyn Van Rheenen
Melbourne Neuropsychiatry Centre, Level 3, Alan Gilbert Building, 161 Barry St, Carlton, Vic 3053, Australia, tamsyn.van@unimelb.edu.au
Binary categorisation of CVD risk factors.

Waist circumference (1)
- low = male ≤94cm, female ≤ 80cm
- high = male >94cm, female >80cm

Dietary saturated fat (2)
- low = < 40
- mod/high = ≥40

Obesity categorised (3)
- Obese = BMI ≥30
- Not obese = BMI<30

Triglycerides (4)
- low = ≤200 mg/dl
- high = >200 mg/dl

Framingham Heart Risk Score (5)
- low = ≤12%
- high = >12%
References