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Dietary patterns, body mass index and inflammation: pathways to depression and mental health problems in adolescents

Wendy H. Oddy[1,2], Karina L. Allen[3], Georgina S.A. Trapp[2,4], Gina L. Ambrosini[4], Lucinda J. Black[2,5], Rae-Chi Huang[2], Peter Rzehak[6], Kevin C. Runions[2], Feng Pan[1], Lawrence J. Beilin[7], Trevor A. Mori[7]

[1] Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000 Australia

[2] Telethon Kids Institute, University of Western Australia, West Perth, Western Australia 6872, Australia

[3] School of Psychology, University of Western Australia, Nedlands, Western Australia 6009, Australia

[4] School of Population Health, University of Western Australia, Nedlands, Western Australia 6009, Australia

[5] School of Public Health, Curtin University, Bentley, Western Australia 6102, Australia

[6] Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, Ludwig-Maximilians Universität München (LMU), Munich, Germany

[7] School of Medicine and Pharmacology, University of Western Australia, Nedlands, Western Australia 6009, Australia

Corresponding Author:

Wendy H. Oddy

Menzies Institute for Medical Research

University of Tasmania

17 Liverpool Street

Hobart, Tasmania 7000

Email: Wendy.Oddy@utas.edu.au; Phone: 61+ 3 6226 7514

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Acronyms:

BDI_Y	Beck Depression Inventory for Youth
BMI	body mass index
CHD	coronary heart disease
FFQ	food frequency questionnaire
hs-CRP	high sensitivity C-reactive protein
SEM	Structural Equation Modelling
y	year
YSR	Youth Self Report

Abstract

Background: Observational studies suggest that dietary patterns may impact mental health outcomes, although biologically plausible pathways are yet to be tested. We aimed to elucidate the longitudinal relationship between dietary patterns, adiposity, inflammation and mental health including depressive symptoms in a population-based cohort of adolescents. **Methods:** Data were provided from 843 adolescents participating in the Western Australian Pregnancy Cohort (Raine) Study at 14 and 17 years (y) of age. Structural equation modelling was applied to test our hypothesised models relating dietary patterns, energy intake and adiposity (body mass index) at 14 y to adiposity and the pro-inflammatory adipokine (leptin) and inflammation (high sensitivity C-reactive protein – hs-CRP) at 17 y, and these inflammatory markers to depressive symptoms (Beck Depression Inventory) and Internalising and Externalising Behavioral Problems (Child Behavior Check List Youth Self- Report) at 17 y. We further tested a reverse hypothesis model, with depression at 14 y as a predictor of dietary patterns at the same time-point. **Results:** The tested models provided a good fit to the data. A 'Western' dietary pattern (high intake of red meat, takeaway, refined foods, and confectionary) at 14 y was associated with higher energy intake and BMI at 14 y, and with BMI and biomarkers of inflammation at 17 y (all $p<0.05$). A 'Healthy' dietary pattern (high in fruit, vegetables, fish, whole-grains) was inversely associated with BMI and inflammation at 17 y ($p<0.05$). Higher BMI at 14 y was associated with higher BMI ($p<0.01$), leptin ($p<0.05$), hs-CRP ($p<0.05$), depressive symptoms ($p<0.05$) and mental health problems ($p<0.05$), all at 17 y. **Conclusion:** A 'Western' dietary pattern associates with an increased risk of mental health problems including depressive symptoms in adolescents, through biologically plausible pathways of adiposity and inflammation, whereas a 'Healthy' dietary pattern appears protective in these pathways. Longitudinal modelling into adulthood is indicated to confirm the complex associations of dietary patterns, adiposity, inflammation and mental health problems, including depressive symptoms.

1 Introduction

Mental health disorders are expected to become one of the most serious global health issues by 2020 (World Health Organization 2005). In many Western populations the lifetime prevalence of mental health disorders is approaching 50% (Begg et al. 2007). Up to half of adult mental health disorders originate before the age of 14 years (y) and a further 25% before the age of 24 y (Kessler, Berglund et al. 2005, Slade, Teesson et al. 2009), indicating that adolescence is a crucial period of biological change relevant to mental health (Lopez, Mathers et al. 2006). In Australia, national survey data show that those most commonly affected by depression, anxiety and substance abuse disorders are young people aged 16-24 y (Slade, Teesson et al. 2009).

In parallel, obesity and related metabolic conditions are of epidemic proportions in both adults and children, particularly in Western countries. Cardiometabolic and mental health disorders share common pathophysiological pathways that may include chronic inflammation, insulin resistance, endothelial dysfunction, hyper-cortisolaemia and abnormal autonomic tone (Gans 2006, Bullo, Casas-Agustench et al. 2007, Tomfohr, Martin et al. 2008). Depression and anxiety are widely acknowledged as independent risk factors for coronary heart disease (CHD) (Goldston and Baillie 2008, Figueredo 2009), and depressive disorders have been associated with features of the metabolic syndrome, including excess adiposity, glucose intolerance and dyslipidaemia (Murabito, Massaro et al. 2013). Results from the 2009-2010 National Health and Nutrition Examination Survey (NHANES) (United States) of almost 6000 participants found that almost 30% of depressed persons had elevated hs-CRP levels and more than 40% met the criteria for the metabolic syndrome (Rethorst, Bernstein et al. 2014). In the NHANES, persons with elevated inflammation were more likely to be obese, highlighting the significant inflammatory and metabolic burden of depression.

Mental health difficulties are frequently reported among overweight and obese individuals (Warschburger 2005), although the relationship may be bi-directional (Kivimaki, Lawlor et al. 2009).

Emerging data point to the inflammatory response as a potential contributor to the pathophysiology of depression (Miller and Raison 2016). A significant proportion of depressed persons show up-regulation of inflammatory markers such as hs-CRP, interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α), and leptin (Raison, Capuron et al. 2006). These inflammatory cytokines can interact with pathophysiologic domains relevant to depression, such as neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity (Dantzer, O'Connor et al. 2008). High levels of plasma inflammatory markers (hs-CRP and IL-6) are also associated with aggression, impulsivity and diagnoses of Intermittent Explosive Disorder (Coccaro, Lee et al. 2014). It has been suggested that chronic inflammation may underlie the association between diet and depression (Lucas, Chocano-Bedoya et al. 2014), since negative health behaviors, such as a poor diet, may lead to both inflammation and depression in susceptible individuals (Kiecolt-Glaser, Derry et al. 2015).

In the Western Australian Pregnancy (Raine) Cohort study, we previously observed positive cross-sectional relationships between higher scores for a 'Western' dietary pattern and increased BMI (Ambrosini, Huang et al. 2010), cardiometabolic risk (Ambrosini, Huang et al. 2010), attention deficit hyperactivity disorder (Howard, Robinson et al. 2011) and higher withdrawal, depression, delinquency and aggressive behaviors (Oddy, Robinson et al. 2009). We extend these previous findings in the same cohort by examining mechanistic pathways between dietary patterns, energy intake, BMI and inflammatory markers, and outcomes of depressive symptoms and mental health. We use prospective structural equation modelling (Hoyle 2012) to explore our hypotheses: 1) that dietary patterns and BMI at 14 y prospectively predict BMI and inflammatory

markers at 17 y, and 2) that inflammation at 17 y predict depressive symptoms and internalizing and externalizing problems at 17 y. In addition, in a reverse hypothesis model, we test whether increased levels of depressive symptoms lead to a poorer diet, increased BMI and inflammation.

2 Materials and Methods

2.1 Study design

In the Western Australian Pregnancy Cohort (Raine) Study, 2,900 women were recruited from King Edward Memorial Hospital antenatal classes and surrounding private practices in Perth, Western Australia between 1989 and 1991 and who were on average 18 weeks pregnant. The criteria for enrolment were gestational age between 16 and 20 weeks, sufficient proficiency in English to understand the implications of participation, an expectation to deliver at the hospital and an intention to remain in Western Australia so that follow-up was possible. Approximately 100 women per month enrolled and a total of 2,868 live births (96%) were available for follow-up (Newnham, Evans et al. 1993). Data were collected from mothers, their partners, and offspring at 18 and 34 weeks gestation, birth, and at one, two, three, six, eight, ten, 14 and 17 y of age. Data from the follow-ups at ages 14 and 17 y were used for the analysis and are presented here. The Raine Study protocol was approved by the ethics committees of King Edward Memorial Hospital for Women and Princess Margaret Hospital for Children, Perth, Western Australia. Informed consent was obtained from the primary caregiver as well as from study participants at 14 and 17 y.

2.2 Dietary patterns

We previously reported dietary pattern derivation at 14 y in this cohort (Ambrosini, Oddy et al. 2009). Briefly, assessments of food and nutrient intake were made at 14 y (n=1631) using a food frequency questionnaire (FFQ) developed by Commonwealth Scientific and Industrial Research Organisation (CSIRO) Australia and using Australian food composition databases. Using the FFQ, we assessed dietary intake over the previous year and estimated serve size information and usual frequency of consumption of 212 foods or dishes in 38 food groups (Ambrosini, Oddy et al. 2009). The FFQ was completed by the parent with the assistance of the adolescent. Participants with an implausible dietary intake (<3,000kj and >20,000kj) were excluded (n=18) prior to

analysis leaving complete data from 1613 FFQ for the principal components analysis (PCA). PCA was applied to reduce the number of observed variables (food intakes from the food frequency questionnaire) into a smaller number of underlying factors or dietary patterns that explain variations in the observed data (Ambrosini, Oddy et al. 2009). The Kaiser-Meyer-Olkin measure of sampling adequacy showed that the food group data were acceptable for factor analysis (KMO=0.80)(SAS 2002-2003). Using PROC FACTOR in SAS (SAS 2002-2003), PCA on all food groups (grams/day) was conducted, and was limited to those factors with an eigenvalue >1. The scree plot was used to identify the number of retainable factors (Abidoye and Eze 2000). Foods failing to load on any factor ($r<0.10$) were removed from the analysis. After applying varimax rotation, two retainable factors, or dietary patterns, were identified and labelled 'Western' and 'Healthy'. Food groups having a loading of 0.30 or more were considered key contributors to each pattern. The 'Western' pattern comprised foods characterised most strongly by take-away and processed foods, red and processed meats, full-fat dairy, fried potatoes, refined grains, confectionary, soft drink, crisps, sauces and dressings. The 'Healthy' pattern was characterised by higher loadings on whole grains, fruit, vegetables, legumes and fish. Each participant received a z-score for each dietary pattern to indicate the degree to which their reported dietary intake reflected these patterns. Combined, the two patterns explained 84% of the common variation (and 21.5% of the total variation) in food intake (Ambrosini, Oddy et al. 2009, Ambrosini, Oddy et al. 2015). Reliability of the dietary patterns was confirmed by a comparison of patterns created from the FFQ and the three-day food record both completed at 14 y (Ambrosini, O'Sullivan et al. 2011).

2.3 Clinical metabolic and mental health measures

2.3.1 Clinical and metabolic measures

At 14 y and 17 y, a trained research assistant weighed and measured participants in light clothing for height and weight using a calibrated stadiometer and electronic chair scales. BMI was

calculated as body weight (kg) / height (m)^2 and treated as a continuous variable. A blood draw was taken at the same time as BMI was measured at 17 y.

At 17 y, venous blood samples were obtained after an overnight fast for the determination of adiponectin (µg/L), leptin (µg/L) and hs-CRP (mg/L) that were measured in the PathWest Laboratory at Royal Perth Hospital (Ridker 2003, Le-Ha, Beilin et al. 2012). hs-CRP was measured by an immunoturbidimetric method on the Architect c16000 Analyser (intra-assay CV 15.96%). Serum leptin was measured by the ACTIVE® Human Leptin ELISA kit (DSL-10-23100, Diagnostic Systems Laboratories, Webster, TX, USA). Acute inflammation was considered to account for hs-CRP >10 mg/L (Ridker 2003) and participants with this clinical indication of acute (or chronic) inflammation were excluded (n= 16) from all analyses. The rationale for exclusion of participants with hs-CRP > 10 mg/L was that those with >10 mg/L were more likely to have an acute and possibly transient response to a transient condition, such as an infection. and was based on recommendations by the American Heart Association (Pearson, Mensah et al. 2003).

2.3.2 Mental health measures

At 14 and 17 y we assessed the Beck Depression Inventory for Youth (BDI-Y)(Beck, Beck et al. 2001) and other internalising and externalising mental health problems using the adolescent Youth Self Report (YSR) (Achenbach 1991, Warnick, Bracken et al. 2007).

The BDI-Y is a well-established and psychometrically sound measure of depression (Beck, Beck et al. 2001) consisting of 20 items relating to feelings experienced over the previous two weeks up to the time of completion. The total raw score is calculated by adding all item scores (possible range 0–60), with higher scores reflecting the presence of more depressive symptoms. This continuous variable was used for structural equation model analyses. In addition, we report the percentage of our study sample with BDI-Y scores in the normal range (score ≤ 16) and those

with scores suggesting at least mild depressive symptoms (score >17), using the recommended clinical cut-points (Beck, Beck et al. 2001).

The YSR is an adolescent self-report version of the Child Behavior Checklist for Ages 4-18 (CBCL/4-18) and consists of 118-items to measure child and adolescent behavior during the previous six months. The Internalising scale captures withdrawn, somatic, depressive, anxious, and inhibited problems whilst the Externalising scale captures aggressive, delinquent, attentional, hyperactive and conduct problems. Standardised T-scores, normalised separately for boys and girls by age for Internalizing and Externalizing Problem scales, were calculated. Higher scores indicate a higher level of emotional and behavioral problems for both measures (Achenbach 1991, Warnick, Bracken et al. 2007).

2.4 Data analysis

We conducted a multivariate linear regression between our variables of interest for testing of our specific hypotheses prior to Structural Equation Modelling (SEM). Potential confounding factors with respect to effects on inflammation were included in the multivariate linear regression analyses (Table 3). These included sex, maternal ethnicity, maternal education, dietary misreporting at 14 y, physical activity level at 14 y, smoking in the past four weeks at 14 y, alcohol consumed in the past six months at 14 y and family income category at 14 y. Longitudinal SEM was applied to test the relationships between dietary patterns, BMI, inflammation, and mental health problems. Both leptin and hs-CRP were log-transformed. No other potential confounding factors with respect to effects on inflammation were considered for exclusion, however two major risk factors for inflammation, body mass index and dietary patterns, were included in the SEM models.

SEM involves estimating a measurement model based on correlation results (Table 3), which specifies relationships between a set of theoretical or latent constructs (e.g., depression) and a set

of measured or observed variables (e.g., questionnaire items designed to assess depressive symptoms), and a structural model which specifies relationships between the latent constructs under investigation (e.g., inflammation and depression). The overall model consists of both the measurement and structural components, and can be further divided into exogenous (predictor) and endogenous (dependent) variables. For our analyses, separate models were run for the three mental health outcome variables of depressive symptoms, Internalising Behavioral Problems, and Externalising Behavioral Problems, all at 17 y.

2.4.1 Measurement models

Measurement models are generally constructed by undertaking factor analysis with the variables (e.g., questionnaire items) measured to assess the construct in question, and then using the four highest loading items as indicator variables (Cole and Maxwell 2003). This was the approach taken for the Healthy and Western dietary patterns constructs (using the four highest loading items on each dimension, as identified in previous analyses) (Ambrosini, Oddy et al. 2009) and depression (using the four highest loading items on the BDI-Y, as identified through PCA undertaken for this work). As there are four subscales contributing to the Internalising Problem scale of the YSR, and four contributing to the Externalising Problem scale of the YSR, these subscales were used as indicator variables for the Internalising and Externalising Problem constructs. For these constructs with four indicator variables (Dietary Patterns, Depression, Internalising and Externalising Problems), estimation of the measurement models included factor analysis estimation of item loadings and error terms for each indicator variable.

For measurement models with a limited number of possible indicator variables, it is not possible for factor analysis to take place and so error terms must be set manually. This applied for BMI (indicated by a single variable: measured BMI), energy intake (indicated by a single variable:

reported kilojoule intake), and inflammation (indicated by two variables: measured hs-CRP and Leptin). For BMI and inflammation, error terms were fixed to the standard error of the item mean, which is consistent with standard practice (Byrne 1998). This equated to 0.14 for BMI at age 14, 0.15 for BMI at age 17, and 0.04 for the two markers of the inflammation pathway. As energy intake was estimated from self-reported dietary intake, the error term for this variable was set higher (=.25) in recognition of the possibility of dietary misreporting. This term was an estimate based on plausible likely error in dietary reporting.

After identifying indicator variables for each construct, confirmatory factor analysis was conducted in LISREL 8.72 for the exogenous and endogenous measurement models. As noted, error terms were fixed for indicators of BMI, energy intake and inflammation. Each set of indicator variables were allowed to co-vary. Exogenous constructs were those that were not predicted by any other construct within the model (e.g., dietary patterns at age 14), whilst endogenous constructs were those that were predicted by at least one other construct (e.g., inflammation, depression). Analyses were conducted using polychoric correlations and covariance matrices, using the maximum likelihood technique (Hoyle 2012).

Measurement models were evaluated in terms of the Goodness of Fit Index (GFI), Adjusted Goodness of Fit Index (AGFI), Normed Fit Index (NFI), Comparative Fit Index (CFI), and Root Mean Square Error of Approximation (RMSEA). For a model to be considered a "good fit", the GFI, AGFI, NFI, and CFI should exceed .90, with values closer to 1.00 being preferable. For the RMSEA, values should be below .05, with values below .10 considered acceptable (Byrne 1998, Kelloway 1998, Raykov and Marcoulides 2006). The Chi square statistic (χ^2) was also examined and should be small relative to degrees of freedom and non-significant if a model does not differ from the observed data. However, χ^2 is strongly influenced by sample size (with significant values more likely with large samples) and is a less useful index than the fit statistics described.

2.4.2 Structural models

After measurement models were estimated, the exogenous and endogenous components of each model were combined and the structural pathways specified. Furthermore, we performed a reverse hypothesis model that positioned 14-year depression as a predictor of 14-year dietary patterns, with progression from there.

Overall structural models were evaluated using the $\chi^2$and the goodness-of-fit indices described above. As the models were not nested (i.e. no one model was a subset of another, because each had different latent and indicator variables), we did not use χ^2 difference tests to statistically compare model fit. It is important to note that no single measure of fit (or non-fit) is sufficient for judging the adequacy or otherwise of a structural equation model. Most fit indices are influenced by sample size and the number and complexity of the specified pathways, and thus need to be interpreted in conjunction with the predictive utility and theoretical grounding of the model in question. It is advisable that fit statistics be interpreted in the context of other models or theories within the research area, so that the relative fit of the model can be ascertained (Byrne 1998, McDonald and Ringo Ho 2002, Goffin 2006).

3 Results

Figure (Fig.) 1 presents the flow diagram of adolescents attending both the 14 and 17 y follow-ups. Complete data, including BDI-Y at 14 y were available for n=843. We used the number with the BDI-Y at baseline. When considering the YSR with complete data n=838 were available for Figs. 3 and 4. Supplementary Table 1 (ST1) in the Online Supplementary Material shows the characteristics of adolescents participating at both 14 y and 17 y compared to non-participants. Participants had mothers who were older at birth and had a higher birthweight compared to non-participants.

Table 1 shows characteristics of study participants by sex. We performed the analyses by stratifying for sex (two group analyses with testing for equality of estimates among the sex groups) and by testing the inclusion of sex as a variable in the SEM model. Neither approach resulted in significantly different findings. We tested for interactions between sex and the key predictor variables prior to conducting SEM, in standard linear regression models. This included interaction terms between BMI and dietary patterns at 14 y in the prediction of BMI at 17 y; between sex and BMI at 17 y in the prediction of inflammation markers at 17 y; and between sex and inflammation markers at 17 y in the prediction of mental health at 17 y. Analyses were repeated by including any smoking in the past four weeks at 14 y and interaction with sex. No significantly different findings were observed. We found no evidence to support significant sex differences, with *p* values for the interaction terms ranging between 0.124 and 0.762. As such, we did not test for sex differences in the overall structural equation models.

Table 2 shows the characteristics of participants who provided complete data at both time-points. Only 3% of study adolescents were smoking at 14 y and only 10% had consumed alcohol in the previous six months, although at 17 y 15% were smoking and 50% were consuming alcohol. Due to the small percentage of participants at 14 y in our study sample who were smoking or

consuming alcohol, estimation and conversion for the full SEM models could not be obtained. As measured by the Beck Depression Inventory at 14 y, 9% had mild, moderate or severe depressive symptoms. AT 17 y 15% had mild or more severe depressive symptoms which was increased by 6% from 14 y. AT 17 y 16% had a clinically concerning internalizing T-Score and 20% had a clinically concerning externalizing score. For inflammation, 14% had hs-CRP levels that were higher than 3 mg/L but for 10 or lower, n=16 were excluded equating to 2% who were excluded due to acute inflammation. We considered maternal ethnicity by hs-CRP as mg/L and conducted an independent sample T-test for hs-CRP by maternal ethnicity. The mean hs-CRP in participants with a Caucasian mother was 1.8365 mg/L and in participants with a non-Caucasian mother, it was 1.1242 mg/L. Following a test for equality of variances, equal variances were not assumed and the difference was significant (p=0.022; 95% CI: -1.319, -0.1056).

Table 3 includes both unadjusted and adjusted linear regression results underpinning the theoretical framework for the SEM. Following adjustment for the confounders (sex, maternal ethnicity, maternal education, dietary misreporting at 14 y, physical activity level at 14 y, smoking in the past four weeks at 14 y, alcohol consumed in the past six months at 14 y and family income category at 14 y), significant associations were shown for most relationships. However, attenuation of the results between leptin and hs-CRP with depressive symptoms following adjustment was observed. Table 4 gives the fit statistics for the SEM.

3.1 Measurement models

All models made use of the same exogenous measurement model, consisting of Healthy dietary pattern, Western dietary pattern, and Kilojoule constructs at 14 y. Based on the factor analysis (Ambrosini, Oddy et al. 2009), the Healthy dietary pattern construct was indicated by the four highest loading variables reflecting intake of yellow and red vegetables, leafy green vegetables, other vegetables, and tomatoes. The Western dietary pattern construct was indicated by the four

highest loading variables reflecting intake of red meat, refined grains, take away, and confectionary (chocolates, sweets).

When confirmatory factor analysis was run for the exogenous measurement model, the Chi square statistic was significant, χ^2 (19) = 68.18, $p < .001$ and fit statistics were good (RMSEA .055; GFI .98; AGFI .96; NFI .92; CFI .94). Item loadings can be seen in Fig. 2 through 4 (with slight variations across each model, due to the reporting of full model statistics). All items loaded significantly on their specified construct ($p<0.01$).

The endogenous measurement models differed according to the measure of mental health used, but all included single indicators for BMI at ages 14 and 17 y, and leptin and hs-CRP at 17 y as markers of inflammation.

The four highest ranked indicators of depression on the BDI-Y for the depressive symptoms model were the items: “I feel like bad things happen to me”, “I think I do things badly”, “I hate myself”, and “I feel sad”. When the measurement model for the depression analyses was specified, the model had good fit statistics χ^2 (18) = 154.35, $p = .001$, RMSEA 0.095; GFI .99; AGFI .95; NFI .99; CFI .99). All items loaded significantly on their specified construct. Results were similar for the internalising and externalising problem models. In both cases, the measurement model was associated with a significant Chi square statistic (χ^2 [18] = 136.35, $p < .001$ for internalising, and χ^2 [18] = 86.22, $p < .001$ for externalising) and fit statistics were good (RMSEA .089; GFI .99; AGFI .96; NFI .98; and CFI .98 for internalising; RMSEA .010; GFI .98; AGFI .90; NFI .97; CFI .98 for externalising). All items loaded significantly on their specified construct.

3.2 Structural models

3.2.1 Depressive symptoms

The complete depressive symptoms model, consisting of the measurement and structural models, is shown in Fig. 2. The Chi square statistic was significant, χ^2 (108) = 278.09, p < .001 and fit statistics were good (Table 4). The Western dietary pattern and energy intake at 14 y were significantly and positively associated with BMI at 14 y, and with BMI, leptin and hs-CRP at 17 y ($p<0.05$). The Healthy dietary pattern was not significantly associated with BMI at 14 y but was significantly and negatively related to BMI and hs-CRP at 17 y ($p<0.05$). BMI at 14 y was significantly and positively associated with BMI and inflammatory markers at 17 y ($p<0.05$). This inflammation was further linked to depressive symptoms at 17 y (Fig. 2).

3.2.2 Internalising problem behaviors

The complete Internalising problem behaviors model, consisting of the measurement and structural models, is shown in Fig. 3. The Chi square statistic was significant, χ^2 (108) = 279.53, p < .001 but fit statistics were good (Table 4). A Western dietary pattern and energy intake at 14 y were significantly and positively associated with BMI at 14 y and with BMI, leptin and hs-CRP at 17 y (all $p<0.05$). The Healthy dietary pattern at 14 y was negatively related to BMI at 17 y. BMI at 14 y was positively associated with BMI at 17 y, which was subsequently associated with leptin and hs-CRP at 17 y (all p,0.05). These in turn were positively associated with Internalising Behavioral Problems.

3.2.3 Externalising problem behaviors

The complete Externalising Problems model, consisting of the measurement and structural models, is shown in Fig. 4. It also showed a significant Chi square value, χ^2 (108) = 276.73, p < .001 and good indicators of fit (Table 4). A Western dietary pattern and energy intake at 14 y were positively associated with BMI at 14 y and BMI, leptin and hs-CRP at 17 y ($p<0.05$). The 14 y

Healthy dietary pattern was significantly and negatively associated with BMI at 14 y, and with BMI, leptin and hs-CRP at 17 y (all $p<0.05$). BMI at 14 y was positively associated with BMI at 17 y, and leptin and hs-CRP at 17 y, and these were positively and significantly associated with Externalising Behavioral Problems at 17 y ($p<0.05$).

3.2.4 Reverse Hypothesis Model

A reverse hypothesis model positioned 14 y depression as a predictor of 14 y dietary patterns, (Fig. 5). Depression at 14 y did not predict 14 y dietary patterns, refuting the hypothesis of a reverse pathway. This model was a worse fit than the original models (e.g., CFI = .63, GFI = .29) (Table 4) and similar results were obtained for internalising and externalising difficulties. We tested depressive affect and externalizing/internalizing behaviors at 14 y as a predictor of these disorders at 17 y. In every model tested, 14 y mental health disorders were a highly significant risk factor for 17 y mental health disorders ($p<0.0001$ – data not shown).

Additional testing

We tested models without adjusting for pathways from kilojoules to 17 y inflammation and 17 y BMI, and the direct pathways from the dietary pattern constructs to 17 y inflammation. Removing these pathways resulted in slight deterioration in model fit and were retained, given their theoretical justification. The results we present in Fig. 2-4 provide the best and most logical test of our hypotheses.

Not all methodologists agree that standardized path-coefficients can be above 1.0 and are valid with suggestions of misspecification or overfitting of the model. Therefore, we tested the model in Fig. 4 without the direct path from 14 y Western Diet (1.46) on 17 y inflammation and without 14 y kilojoule intake -> (1.28) on 17 y inflammation. These models were a poorer fit without the pathways. Regarding standardised coefficients >1, such coefficients are possible if other model parameters are appropriate (Byrne 1998) and we note this difference in the figure captions.

4 Discussion

4.1 Main findings

This is the first study to show that pathways of diet and BMI were linked to inflammation and, in turn**,** mental health disorders in adolescents at 17 y. We have identified biologically plausible pathways between dietary patterns, adiposity, inflammation, and depression as well as internalising and externalising problem behaviors, confirming our hypothesised relationships. Higher BMI at 14 y was correlated with higher BMI, higher leptin and hs-CRP, depressive symptoms and mental health disorders at 17 y. A Western dietary pattern indirectly associates with an increased risk of mental health problems including depressive symptoms, in adolescents through biologically plausible pathways of adiposity and inflammation, and a 'Healthy' dietary pattern appears protective in these pathways.

4.1.1 Diet, body mass index, inflammation and mental health

We have previously shown that a Western dietary pattern at 14 y was associated with increased energy intake and higher BMI at 14 y (Ambrosini, Huang et al. 2010), and independently with hs-CRP at 17 y. The Healthy pattern was mediated through adiposity and inflammation with a healthier dietary pattern, resulting in inverse associations with adiposity and inflammation. Dietary patterns appear to influence inflammation both directly and indirectly through BMI. Furthermore, the associations between diet, adiposity and inflammation are stronger than between inflammation and mental health, which is understandable given the multifactorial aetiology of mental health disorders. Although there is strong evidence that inflammation precedes depression, some studies have shown bidirectional effects (Irwin and Miller 2007, Gall, Sanderson et al. 2016). We did not show effects of depressive symptoms on diet quality but we did show bidirectional effects from depression to adiposity and inflammation in Fig. 5, and that mental health problems at 14 y were a significant risk factor for mental health problems at 17 y.

Obesity and mental health problems share inflammation as a common link (Shelton and Miller 2010) and, in our analysis, indices of inflammation were positively associated with all mental health outcomes, particularly depressive symptoms. Although our results of inflammation and mental health outcomes were attenuated in multivariate analyses, they continued to be in a positive direction of effect. Diets that promote inflammation also promote adiposity and are high in refined starches, sugar, saturated fats, and low in fibre, vegetables and omega-3 fatty acids (Galland 2010). Others have shown a Western diet high in red and processed meat, confectionary and refined grains associated with higher hs-CRP compared with a healthy dietary pattern characterised by fruit, vegetables, legumes, fish and whole grains (Nanri, Moore et al. 2007). Therefore, inflammation-enhancing diets may contribute to depressive symptoms (Kiecolt-Glaser 2010) and other mental health problems. Refined starches and sugar can rapidly alter blood glucose and insulin levels (Giugliano, Ceriello et al. 2008) and postprandial hyperglycaemia can increase free radical production and pro-inflammatory cytokines, accelerating and stimulating depressive symptoms (Kiecolt-Glaser 2010), and potentially increasing irritability and aggression (Zalcman, Siegel. 2006). Depressive symptoms and hs-CRP have been positively associated in population as well as clinical studies, with a dose-response relationship observed (Howren, Lamkin et al. 2009). Less is known of the link between externalizing problems and inflammatory markers, although our findings support prior work showing links between hs-CRP and aggression (Coccaro, Lee et al. 2014).

4.1.2 Obesity and inflammation

Obesity has been characterised as a state of chronic inflammation because IL-6, TNF-α, hs-CRP and leptin (Dandona, Aljada et al. 2004) are elevated and up to 30% of IL-6 may be derived from adipose tissue. Women with greater central adiposity had larger inflammatory responses to a laboratory stress test than their leaner counterparts (Dandona, Aljada et al. 2004). Adiposity has also been associated with elevated levels of IL-6 and hs-CRP in depressed people (Miller, Maletic

et al. 2009). As adiposity increases, leptin signals the release of hs-CRP from the liver (Jialal, Devaraj et al. 2004), increasing peripheral cytokines and leading to depressive symptoms, aggravating the process of adipose-induced inflammation further. High energy intake in the diet leads to increased accumulation of lipids in adipocytes resulting in an increased release of Monocyte Chemoattractant Protein-1 (MCP-1), a chemoattractant that increases the infiltration of macrophages into adipose tissue (Shelton and Miller 2010). Both adipocytes and macrophages release inflammatory mediators such as IL-6, TNF-α and leptin into the peripheral circulation and leptin has wide ranging effects on the immune response (Miller, Freedland et al. 2003). Others have speculated that fat mass stimulates low level inflammation independently through the hypothalamic-pituitary-adrenal axis (HPA) via direct and feedback interactions among the hypothalamus, the pituitary gland and the adrenal glands (Waelput, Brouckaert et al. 2006). These interactions play a multiplicative role rather than acting as a confounder in mental health problems.

4.1.3 Inflammatory cytokines and depressive symptoms

Extant clinical evidence is restricted to situations where patients are exposed to high doses of inflammatory cytokines due to medical treatment such as cancer, whereby patients routinely develop depressive symptoms. Exposure to inflammatory mediators can produce a constellation of sickness behaviors (Dantzer, O'Connor et al. 2008, Shelton and Miller 2010). In a prospective study, high levels of IL-6 and hs-CRP measured at baseline predicted increased depressive symptoms over a five year period (van den Biggelaar, Gussekloo et al. 2007). A 'Western' diet may lead to increased hs-CRP and pro-inflammatory responses to high fat meals exaggerated by obesity, pushing elevated levels higher (O'Keefe, Gheewala et al. 2008).

4.1.4 Diet and inflammation

Nutrients such as magnesium, fibre, ω-3 polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids, flavonoids, and carotenoids from food associate with a Healthy diet and decreased levels of inflammatory markers, whereas saturated- and trans fatty acids, high-GI carbohydrates, and a high ω-6/ω-3 PUFA ratio associate with a Western diet and increased levels of inflammation (Galland 2010). Habitual intake of a Western dietary pattern may exacerbate low-grade systemic inflammation. The direct and indirect associations between dietary patterns, obesity and inflammation observed in our study are speculated to be partially due to diet and not solely to BMI, although further research is needed around this possibility.

4.2 Strengths and limitations

The prospective design, community sample and adequate statistical power to measure outcomes are clear strengths of the Raine study. Extensive efforts were made to maximise participation rates and minimise loss-to-follow up. Our follow-up rates were comparable or better than similar studies (Wolke, Waylen et al. 2009). While the loss of more disadvantaged participants is expected, the original cohort over-sampled socially-disadvantaged mothers for this reason (Li, Kendall et al. 2008).

A major strength of our study is that three mental health measures were collected (the BDI-Y, the YSR Internalising scale, and the YSR Externalizing scale), allowing multiple domains of mental health to be assessed in a large sample in a timely manner. A recent review of child and adolescent self-report questionnaires (Deighton, Croudace et al. 2014) demonstrates our measures are reliable and valid. However, there is the possibility of under- or over-reporting of symptoms using self-report methods: future research focusing on clinically diagnosed disorders would add to our study. Dietary intake was also self-reported and it is well known that overweight and obese individuals under-report dietary intake more than healthy weight individuals (Black 2000).

Although we could not include dietary misreporting in our structural equation models due to model non-convergence, we limited our analysis to individuals with plausible energy intakes (Ambrosini, Oddy et al. 2009).

We collected data on depressive affect and externalizing/internalizing behavior at 14 y as well at 17 y. However, including 14 y mental health variables in the models resulted in testing for effects of diet, BMI and inflammation on changes in mental health from 14 y to 17 y. However, in every model tested 14 y mental health problems were a significant risk factor for 17 y mental health problems. In our study, we sought to test a specific hypothesized model of how different factors at 14 y (dietary patterns, BMI) and 17 y (BMI, inflammation) may interact to increase the risk of depressive symptoms and internalizing/externalizing problems in later adolescence, at 17 y. Further, the final pathways of these models (inflammation at 17 y to mental health at 17 y) are cross-sectional in nature, which we suggest, reduces the requirement for prior adjustment of 14 y mental health.

A strength of structural equation modelling is that the analysis tests an overall model of specific, hypothesized relationships between multiple variables (Byrne 1998). While we attempted to control for relevant potential confounders, the observational nature of the study means that residual confounding cannot be ruled out. Other drug use, hormones related to menarche, hormonal treatments or pregnancy are important but remain unexplored in our analysis. We acknowledge that the hypothesised pathways may be due to underlying genetic or common environmental factors and that establishing true causality is difficult and beyond the scope of our analyses.

5 Conclusion

Scientific work on the relationship of inflammation to mental health problems is still in its infancy, and this study provides an important contribution by mapping out the relationship of diet,

adiposity, inflammation and mental health disorders. The Western dietary pattern associates with increased obesity and increased chronic inflammation (Esposito and Giugliano 2006) and the healthy dietary pattern associates with less obesity and inflammation, as we have seen in the analysis presented here. A Western dietary pattern indirectly associates with an increased risk of mental health problems, including depressive symptoms in adolescents, through biologically plausible pathways of adiposity and inflammation, whereas a Healthy dietary pattern appears protective in these pathways. A reverse hypothesis was not supported but further longitudinal modelling into adulthood is indicated. An understanding of the co-morbidity of depression and other mental health disorders with obesity may provide a clearer understanding of the benefits of improved diet as a target for preventive strategies. We speculate that a diet high in red and processed meat, takeaway and refined foods, soft drink and confectionary contributes to a pathway involving adiposity, inflammation and depressive, internalising and externalising symptoms in adolescents. We further speculate that a diet high in fruit, vegetables, legumes, fish and wholegrains contributes to a pathway of less adiposity, inflammation and mental health problems in adolescents. A potential tri-directional relationship between adiposity, inflammation and depression should not be excluded (Stewart, Rand et al. 2009) with dietary and nutritional factors significantly influencing and impacting these relationships. Future investigation is warranted to describe the links between diet (food components and nutrients), adiposity, inflammation, depression and other mental health disorders.

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Figure Legends

Fig. 1. Flow diagram of adolescents attending the 14 and 17 year (y) follow-ups of the West Australian Pregnancy Cohort (Raine) Study

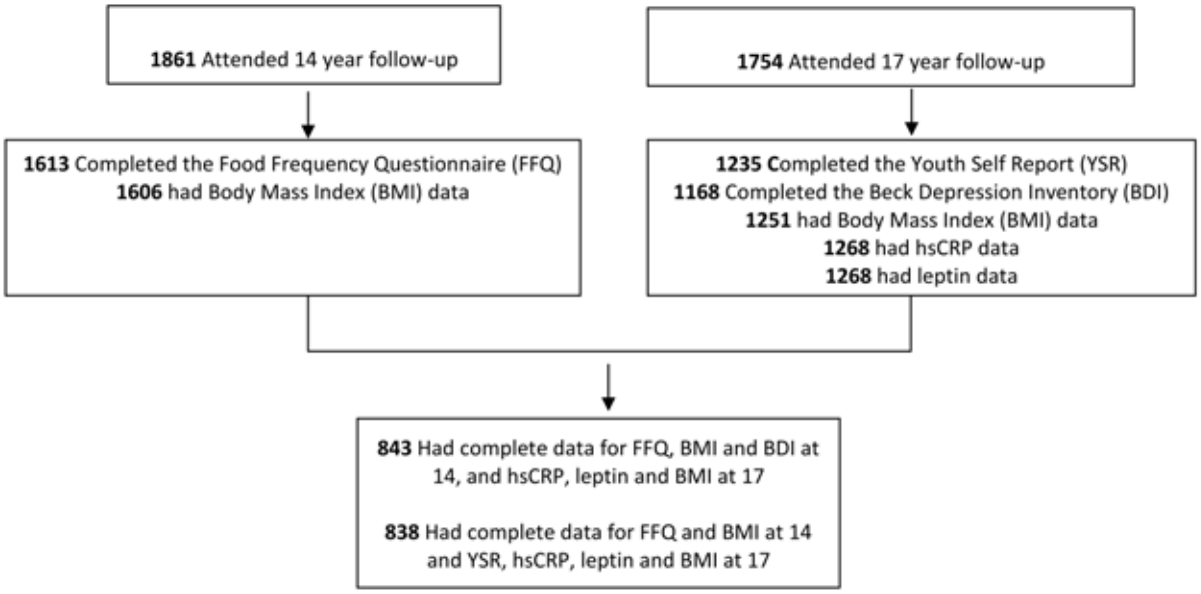
Fig. 2. Full structural equation model for the relationships between 14 year (y) dietary patterns, 14 y Body Mass Index (BMI), 17 y BMI, 17 y inflammation, and 17 y depressive symptoms. Square boxes depict observed variables and bolded ellipses depict latent constructs. Values reflect standardised coefficients and standard error terms, and values in bold are significant (* $p < .05$, ** $p < .01$). In contrast to other statistical techniques, standardised coefficients can exceed one in structural equation modelling. Summary of Fig. 2: The Western dietary pattern and energy intake at 14 y were significantly and positively associated with BMI at 14 y, and with BMI, leptin and hs-CRP at 17 y ($p<0.05$). The Healthy dietary pattern was not significantly associated with BMI at 14 y but was significantly and negatively related to BMI and hs-CRP at 17 y ($p<0.05$). BMI at 14 y was significantly and positively associated with BMI and inflammatory markers at 17 y ($p<0.01$). This inflammation was further linked to depressive symptoms at 17 y ($P<0.05$).

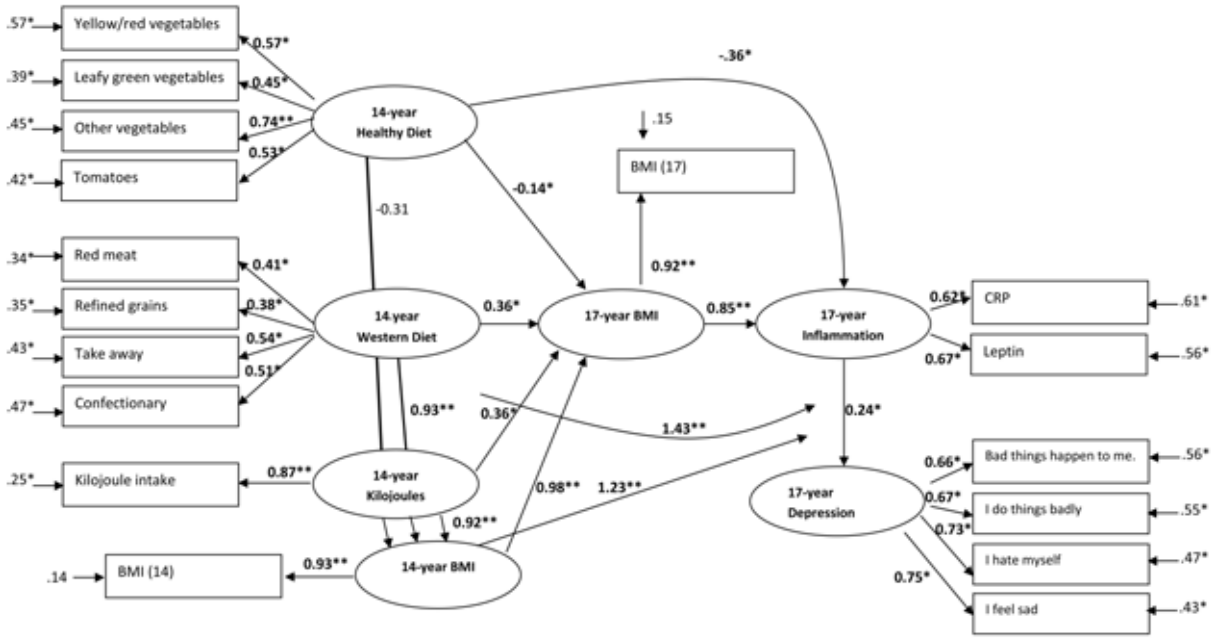
Fig. 3. Full structural equation model for the relationships between 14 year (y) dietary patterns, 14 y Body Mass Index (BMI), 17 y BMI, 17 y inflammation, and 17 y internalising problems. Square boxes depict observed variables and bolded ellipses depict latent constructs. Values reflect standardised coefficients and standard error terms, and values in bold are significant (* $p < .05$, ** $p < .01$). In contrast to other statistical techniques, standardised coefficients can exceed one in structural equation modelling. Summary of Fig. 3: The Western dietary pattern and energy intake at 14 y were significantly and positively associated with BMI at 14 y, and with BMI, leptin and hs-CRP at 17 y ($p<0.01$). The Healthy dietary pattern was not significantly associated with BMI at 14 y but was significantly and negatively related to

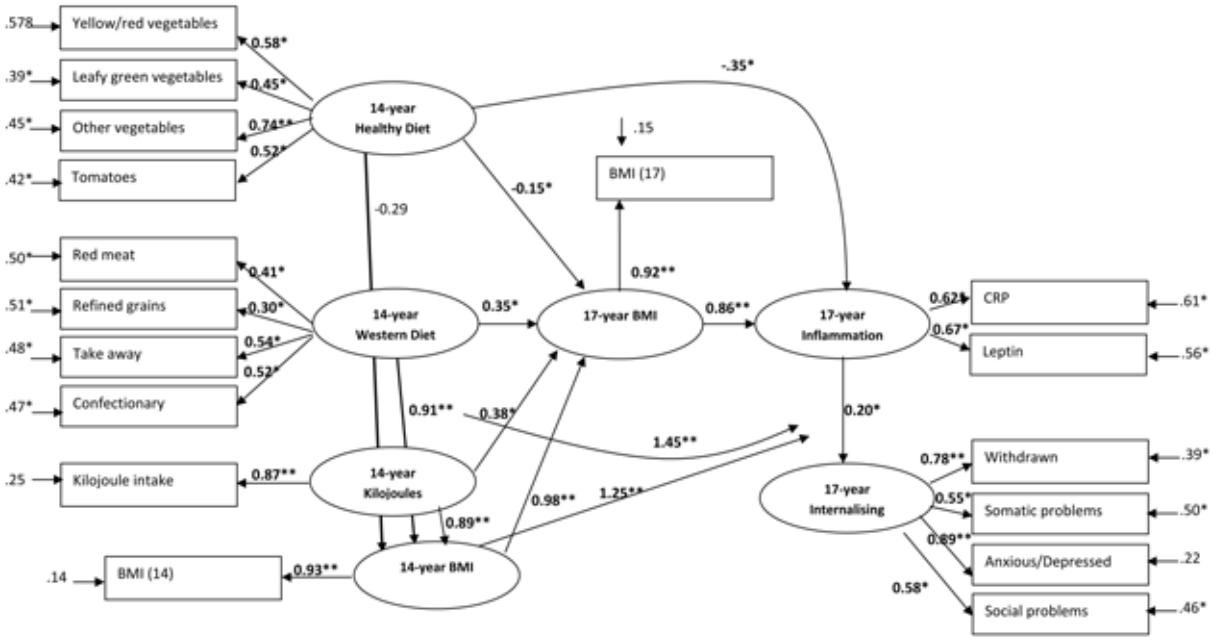
BMI and hs-CRP at 17 y ($p<0.05$). BMI at 14 y was significantly and positively associated with BMI and inflammatory markers at 17 y ($p<0.01$). This inflammation was further linked to Internalising problems at 17 y ($p<0.05$).

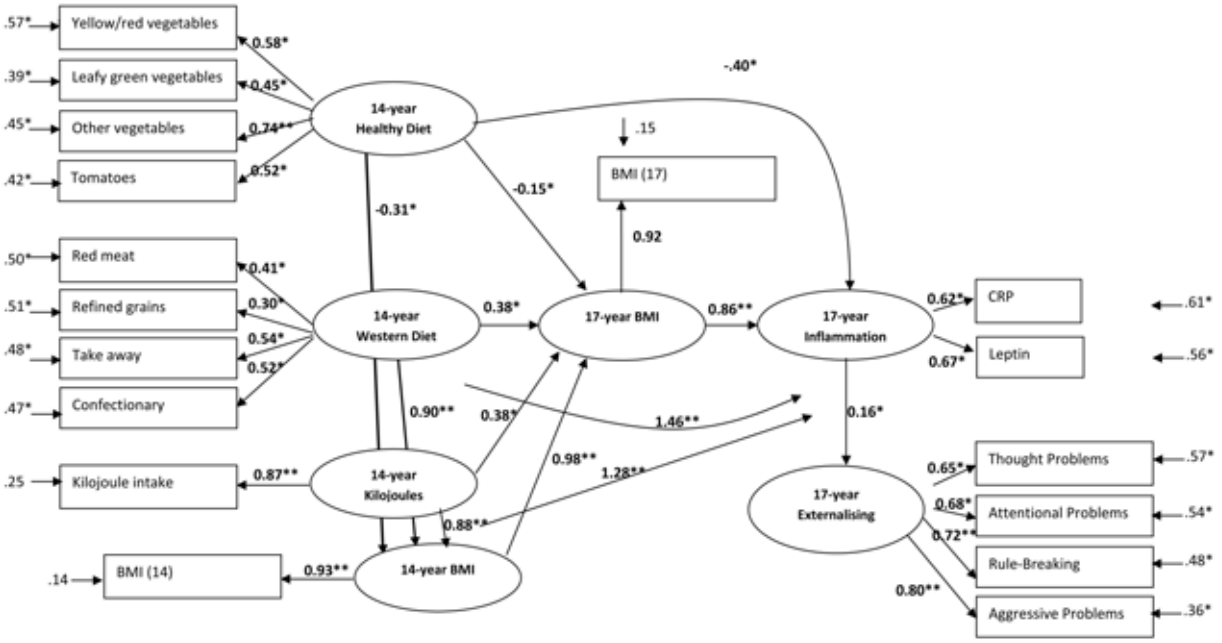
Fig. 4. Full structural equation model for the relationships between 14 year (y) dietary patterns, 14 y Body Mass Index (BMI), 17 y BMI, 17 y inflammation, and 17 y externalising problems. Square boxes depict observed variables and bolded ellipses depict latent constructs. Values reflect standardised coefficients and standard error terms, and values in bold are significant (* $p < .05$, ** $p < .01$). In contrast to other statistical techniques, standardised coefficients can exceed one in structural equation modelling. Summary of Fig. 4: The Western dietary pattern and energy intake at 14 y were significantly and positively associated with BMI at 14 y, and with BMI, leptin and hs-CRP at 17 y ($p<0.01$). The Healthy dietary pattern was not significantly associated with BMI at 14 y but was significantly and negatively related to BMI and hs-CRP at 17 y ($p<0.05$). BMI at 14 y was significantly and positively associated with BMI and inflammatory markers at 17 y ($p<0.01$). This inflammation was further linked to Externalising problems at 17 y ($p<0.05$).

Fig. 5. Structural model showing the relationships between 14 year (y) depressive symptoms, 14 y dietary patterns, 17 y dietary patterns, and 17 y Body Mass Index (BMI) and inflammation mediator and markers. The ellipses depict latent constructs. Values reflect standardised coefficients, and values in bold are significant (* $p < .05$, ** $p < .01$). Summary of Fig. 5: Depression at 14 y did not predict 14 y dietary patterns, refuting the hypothesis of a reverse pathway. This model was a worse fit than the original models (e.g., CFI = .63, GFI = .29) (Table 4) and similar results were obtained for internalising and externalising behavioral problems.









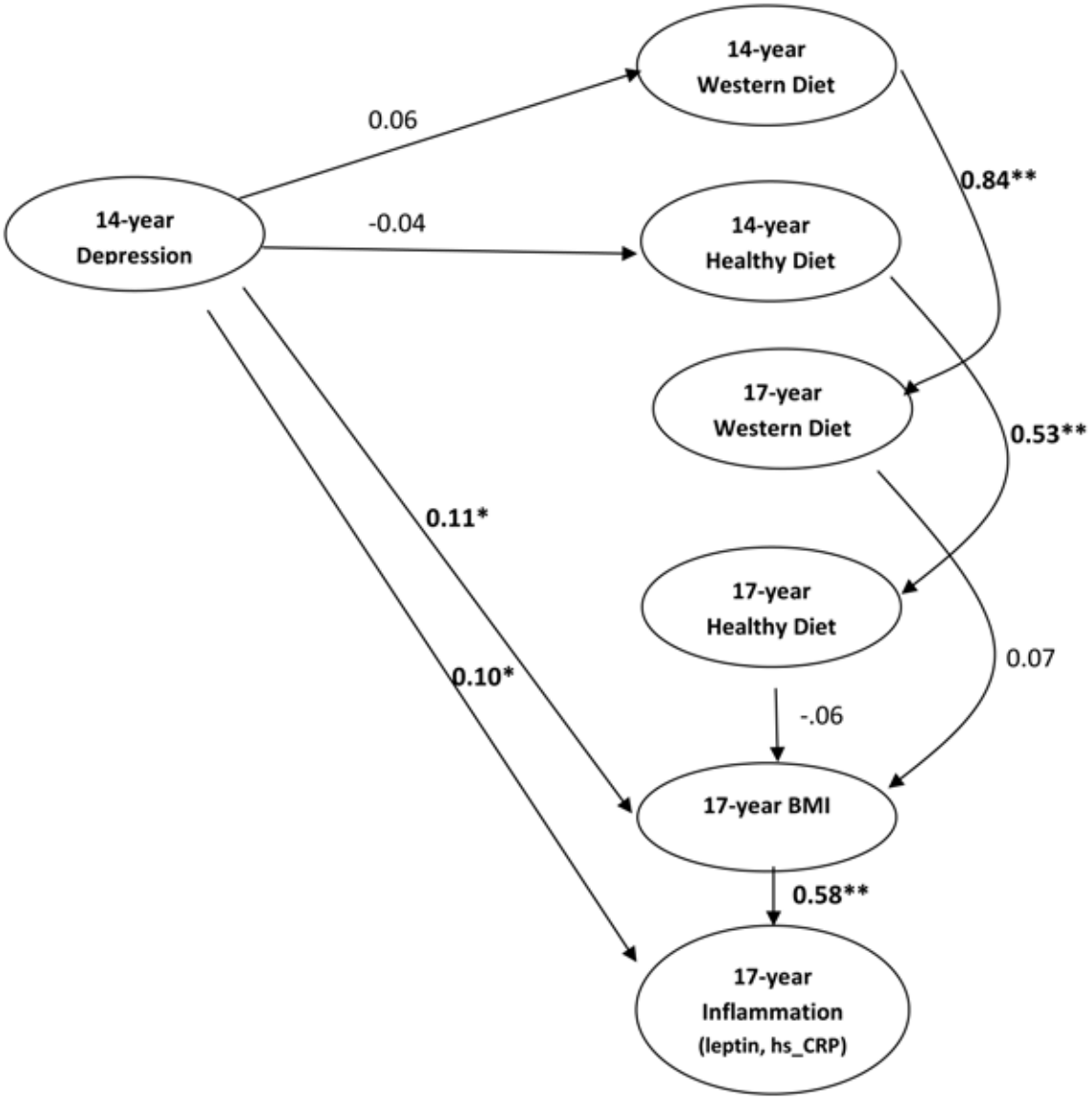

14-year Depression
14-year Western Diet
14-year Healthy Diet
17-year Western Diet
17-year Healthy Diet
17-year BMI
17-year Inflammation (leptin, hs_CRP)
0.06
-0.04
0.84**
0.53**
0.11*
0.10*
0.07
-.06
0.58**

Table 1: Characteristics of Raine Study participants at 14 years by total, female and male

Exposures at 14 years	**Total** N=843 %	**Female** (N=429: 51%) %	**Male** (N=414: 49%) %
Maternal ethnicity			
Caucasian	88	87	89
Non-Caucasian*	12	13	11
Maternal education			
<12 years	28	29	27
≥12 years	72	71	73
Dietary misreporting			
Under-reporting	26	40	12
Plausible reporting	64	57	71
Over-reporting	10	3	17
Physical activity level			
once a month or less	10	14	6
1-3 times week	57	60	53
4 + times week	33	26	41
Smoking in the past four weeks			
No	97	96	98
Yes	3	3	2
Alcohol consumed in the past six months			
No	87	87	87
Yes	10	10	10
Family income category			
< $40,000	25	28	23
$40,001 to $60,000	20	23	18
$60,001 to $104,000	33	29	36
>$104,000	20	18	21

***** mainly Asian

Table 2: Characteristics of Raine Study participants (at 14 and 17 years) who provided complete data [n=843] for the Structural Equation Modelling

	Mean (SD) unless stated
Dietary intake	
Healthy pattern z score at 14 years	0.002 (0.817)
Western pattern z score at 14 years	-0.08 (0.832)
Energy intake at 14 years (KJ/day)	9431.02 (2939.46)
BMI	
BMI at 14 years (kg/m^2)	21.3 (4.2)
BMI at 17 years (kg/m^2)	22.9 (4.4)
Inflammation (Ridker 2003, Fantuzzi 2005)	
17 year Leptin ug/L	18.2 (20.5)
17 year hs-CRP mg/L	1.7 (5.2)
Low grade inflammation (hs-CRP 2-3) %	5.3
Inflammation[b] (hs-CRP > 3) %	13.9
Mental health[a]	
Beck Depression Inventory at 14 years (Beck et al. 2001)	6.38 (6.79)
Normal range %	91.5
Mild or greater depressive symptoms %	8.5
Beck Depression Inventory at 17 years (Beck et al. 2001)	6.46 (6.93)
Normal range %	85.0
Mild or greater depressive symptoms %	15.0
YSR Internalising T-score at 17 years	48.8 (10.7)
Clinically concerning YSR Internalising T-score %	16.2
YSR Externalising T-score at 17 years	51.2 (10.3)
Clinically concerning YSR Externalising T-score %	19.9

[a]Higher scores indicate a higher level of emotional and behavioural problems.
YSR: Youth Self Report; BMI: Body Mass Index, M: Mean, SD: Standard Deviation.
[b] hs-CRP > 10 were excluded n=16

Table 3: Multivariate linear regression[§] between interested variables for testing of hypotheses prior to Structural Equation Modelling

	Kilojoules at 14 y	BMI at 14 y	BMI at 17 y	hs-CRP^ at 17 y	Leptin^ at 17 y	BDI at 17 y	Internalising problems at 17 y	Externalising problems at 17 y
Healthy dietary pattern								
Unadjusted	.234**							
[§]Adjusted	.113**							
Western Dietary pattern								
Unadjusted	.774**							
[§]Adjusted	.445*							
Kilojoule (kj) intake at 14 years (y)								
Unadjusted		-.099**						
[§]Adjusted		.419**						
Body mass index (BMI) at 14 y								
Unadjusted			.877**	.519**				
[§]Adjusted			.880**	.457**				
BMI at 17 y								
Unadjusted				.410**				
[§]Adjusted				.366**				
hs-CRP^ at 17 y								
Unadjusted					.399**	.101*		
[§]Adjusted					.255**	.031		
Leptin^ at 17 y								
Unadjusted						.245**		
[§]Adjusted						.058		
Beck Depression Inventory (BDI) at 17 y								
Unadjusted							.626**	.395**
[§]Adjusted							.667**	.370**
Internalising problems at 17 y								
Unadjusted								.364**
[§]Adjusted								.364**

**Standardised Beta Coefficient is significant at p< 0.0001 level; *Standardised Beta Coefficient is significant at p< 0.01 level; [§]adjusted for sex, maternal ethnicity, maternal education, dietary misreporting at 14 y, physical activity level at 14 y, smoking in the past four weeks at 14 y, alcohol consumed in the past six months at 14 y and family income category at 14 y: ^ both leptin and hs-CRP were log-adjusted. Acronyms: kj=kilojoules; y=years; BDI= Beck Depression Inventory; BMI= body mass index; hs-CRP=high sensitivity C-reactive protein.

Table 4: Fit statistics for the tested structural equation models and the reverse hypothesis model*

	RMSEA	GFI	AGFI	NFI	CFI
Depression	.043	.96	.95	.94	.96
Internalising problems	.043	.96	.94	.94	.95
Externalising problems	.044	.96	.95	.94	.96
Reverse hypothesis model	.688	.29	.33	.71	.63

Note. RMSEA = Root Mean Square Error of Approximation, GFI = Goodness of Fit Index, AGFI = Adjusted Goodness of Fit Index, NFI = Normed Fit Index, CFI = Comparative Fit Index. *standardised coefficients can exceed 1 in structural equation modelling.

Highlights

- Diet and adiposity are linked to inflammation and mental health problems in adolescents
- A Western dietary pattern associates with increased depression risk in adolescents
- A 'Healthy' dietary pattern protects against depression in adolescents through reduced BMI and associated inflammation