DIET AND SLEEP IN AUSTRALIAN MIDDLE AGED AND ELDER MEN

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Submitted in fulfilment of the

Degree of Doctor of Philosophy

The University of Adelaide

January 2017

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ABSTRACT

Optimal sleep duration and quality sleep are an important cornerstone for good health. Poor sleep can lead to a series of adverse consequences in metabolic and immune systems, as well as in mortality. Research into the effects of diet on sleep have mainly focused on single macronutrients and laboratory studies. Not yet explored are the complex interactions between dietary intake and chronic disease, psychosocial and lifestyle factors in relation to sleep at the population level.

This thesis aims to investigate the complexity of the association between dietary factors and sleep outcome (objective and subjective measures) middle aged and elderly Australian men. Data used in the thesis were from the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study, established to determine the explanatory variables, and help with treatment and preventive measures, for the development of chronic diseases in men.

The studies undertaken in this thesis firstly examined the association between macronutrients intake and the risk of sleep apnoea and self-reported sleep symptoms in men aged 35-80 years old. This study found that compared with the lowest quartile of fat intake, the highest quartile was associated with increased risks of daytime sleepiness and sleep apnoea events during the night. No associations were observed between carbohydrate and protein and sleep parameters.

The studies undertaken secondly determined dietary patterns in the same population, and explored the association between these dietary patterns and sleep parameters. Three dietary patterns were identified: the prudent pattern that is characterized by fruits, vegetables and legumes and the western pattern that is characterized by processed meat, snacks, red meat and take-away foods, and the mixed pattern that is a combination of these two patterns. The

prudent pattern is associated with faster sleep onset, but no other associations were found between dietary patterns and sleep outcomes.

Dietary effects on inflammation have been widely studied, but no studies have linked dietary inflammation with sleep disorders. The final study examined the association between nutrient patterns and inflammation, as well as the interactions between nutrient patterns and obstructive sleep apnoea (OSA), lifestyle factors, and chronic diseases. An animal-sourced pattern (characterized by animal protein, cobalamin, cholesterol and omega-6) was positively associated with inflammation, while a plant-sourced pattern (characterized by beta-carotene, vitamin A, lutein and zeaxanthin) was inversely associated with inflammation. The association between the plant-sourced pattern and CRP was stronger in participants with sedentary lifestyle, high level of OSA, but without diabetes or dyslipidaemia. No associations were found between the vitamin B and folate pattern (characterized by total folate, thiamine, riboflavin and niacin) and inflammatory markers.

These studies confirmed the associations between dietary factors and sleep parameters at the population level. A general low fat and plant-based diet may improve sleep. In addition, a comprehensive understanding among diet, sleep disorders and inflammation and chronic diseases is highlighted. These findings have significant implications in public health and clinical management of chronic inflammation.

DECLARATION

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

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Yingting Cao

Date 19/01/2017

ACKNOWLEGEMENTS

Three years of adventure moving from Sweden to Australia has almost gone and many thanks I need to express. Firstly, great thanks to my husband Zhuo Jiang. Without your support, I could not have started this PhD journey from the beginning. Being separate is a pain for both of us, although sometimes it is even tougher, we have supported each other untill today, which is amazing.

Great thanks to my supervisors Associate Professor Zumin Shi, Professor Anne Taylor and Professor Gary Wittert. To Zumin, thank you for your great help for both my study and life. Your kindness, patience and expertise have been invaluable. To Anne, thank you for your great trust and support for both my study and family, for your humanistic care, as a boss and a senior and for your patience and efforts in reviewing my work. To Gary, thank you for your invaluable advice, for your efforts and time you have dedicated to improving my work and the inspiration that encourages me to think more and deeply.

To my colleagues at Population Research and Outcome Studies, thank you all for a nice and friendly environment. I would particularly like to thank Eleonora Dal Grande, for your advice and your experience of preparing a thesis; and Janet Grant for your help with the dataset, and thanks to both of you for the time and effort you spent in improving my English.

A big thank you to my parents. Your endless support enables me to set my goals and be determinant. Being away from home is tough for you; I appreciate your great understanding, and your restrained parents' thoughts of love thousand miles away from Australia.

I would also like to thank the NWAHS and the MAILES participants, without you, the work we do is impossible.

RESEARCH PRESENTATIONS

- **Cao Y,** Wittert G, Taylor A. W, & Shi Z. (Oral Presentation): *Dietary pattern and sleep: cross-sectional associations in a cohort of community dwelling men.* **Adelaide Sleep Retreat, University of South Australia, Adelaide, 2014**
- **Cao, Y.**, Wittert, G., Taylor, A. W., Adams, R., & Shi, Z. (Poster presentation): *Associations between Macronutrient Intake and Obstructive Sleep Apnoea as Well as Self-Reported Sleep Symptoms: Results from a Cohort of Community Dwelling Australian Men*. **12th Asian Congress of Nutrition, Yakohama, Japan, 2015**
- **Cao Y,** Wittert G, Taylor A. W., Adams R, & Shi, Z. (Oral presentation): *Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men.* **Freemasons Foundation Centre for Men's Health, Adelaide, 2015**
- **Cao, Y.**, Wittert, G., Taylor, A. W., Adams, R., & Shi, Z. (Poster presentation): *Associations between Macronutrient Intake and Obstructive Sleep Apnoea as Well as Self-Reported Sleep Symptoms: Results from a Cohort of Community Dwelling Australian Men*. **Research showcase, South Australian Health and Medical Research Institute, Adelaide, 2015**
- **Cao Y,** Wittert G, Taylor A. W., & Shi Z. (Oral & Poster presentation): *Dietary pattern and sleep: cross-sectional associations in a cohort of community dwelling men.* **Sleep Down Under, Melbourne, 2015**
- **Cao Y,** Wittert G, Taylor A. W., Adams R, & Shi, Z. (Poster presentation): *Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men.* **38th ESPEN Congress, Copenhagen, Denmark, 2016**

MEDIA COVERAGE

- Fatty diet linked to daytime sleepiness, SBS the world news, 20 April, 2016
- This may be why you are always sleepy, Herald Sun, 20 April, 2016
- University of Adelaide research suggests a fatty diet could be linked to sleep disorders in men, The (Adelaide) Advertiser, 20 April, 2016
- A high-fat diet may lead to daytime sleepiness, New York Times/Well/Eat, 21 April, 2016
- New reason to eat well, Network 10, Adelaide (TV interview), 21 April, 2016
- Too much fat could short circuit your brain's sleep cycle, Medical Daily, 27 April, 2016
- Radio interview, Adelaide 891 ABC, 22 April, 2016
- Radio interview, Sydney 2UE, 25 April, 2016

ABBREVIATIONS

AHI	Apnoea-Hypopnea Index
ATC	Anatomical Therapeutic Chemical
BDHQ	Brief-Type Self-Administered Diet History Questionnaire
BMI	Body Mass Index
CAD	Coronary Artery Disease
CATI	Computer assisted telephone interview
CHF	Congestive Heart Failure
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DIS	Difficulty In Initiating Sleep
DMS	Difficulty In Maintaining of Sleep
DQES	Diet Questionnaire for Epidemiological Studies
EEG	Electroencephalogram
EOG	Electrooculogram
EMG	Electromyogram
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
FAMAS	Florey Adelaide Male Ageing Study
FFQ	Food frequency questionnaire

HDL	High-density lipoprotein
IL-1	Interleukin-1
IL-6	Interleukin-6
LDL	Low-density lipoprotein
LV	Left Ventricle
GI	Glycaemic Index
GL	Glycaemic Loading
MAILES	Men Androgen Inflammation Lifestyle Environment and Stress
MLR	Multinominal Logistic regression
NHANES	National Health and Nutrition Examination Survey
NWAHS	North West Adelaide Health Study
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PCA	Principal Component Analysis
PSG	Polysomnography
PSQI	Pittsburg Sleep Quality Index
RRR	Reduced Rank Regression
SES	Socioeconomic Status
SOL	Sleep Onset Latency
STOP	Snore, Tiredness during daytime, Observed apnoea and high blood Pressure

TNF	Tumour Necrosis Factor
TST	Total Sleep Time
UK	United Kingdom
USA	United States of America
WASO	Wake After Sleep Onset

CHAPTER 1 INTRODUCTION

1.1 Background

Sleep is a state characterized by periodic, reversible loss of consciousness, reduced sensory and motor functions, internally generated rhythmicity, homeostatic regulation, and a restorative quality that cannot be duplicated by rest without sleep or by any food, drink or drug [1]. Sleep is important for human beings as it is essential for neurological and physiologic processing in order to maintain survival [2].

Optimal sleep duration for adults (18-64 years) is recommended as 7-9 hours according to the latest guideline from the American National Sleep Foundation 2015 [3]. Sleep quality, which may reflect general sleep experience, includes sleep quantity, wakefulness, feeling of refreshment and daytime sleepiness [4].

Nearly 30% of adults reported a sleep duration ≤6 hours/day in 2005-2007 according to the National Health Interview Survey in the United States of America (USA) [5]. A study from New South Wales in 2008 suggested 18% of the subjects had sleep duration less than 6.5 hours/day [6]. Similarly, the burden of poor sleep quality has been found to be high (15-50%) in different populations [7-9]. In a Chinese elderly rural sample of 2700 residents (mean age 68) between 2009-2010, 49.7% reported poor sleep quality [8]. The one-month point prevalence of poor sleep quality in 5924 Japanese white-collar employees in 2000 was approximately 30%-45% [10].

A number of studies have reported the links between impaired sleep and metabolic syndrome [11], diabetes [12], cardiovascular disease (CVD) [13] and mortality [14]. Inadequate sleep has also been found to impair immune and antioxidant systems within the body [2]. Deprivation of sleep has been suggested to affect metabolic system adversely (Figure 1.1) [15]. Changes in the activity of neuroendocrine systems induced by sleep loss may mediate the detrimental metabolic effects via favouring neuro behavioural outcomes

such as increased appetite and enhanced sensitivity to food stimuli, and ultimately result in a surplus in energy intake [15].

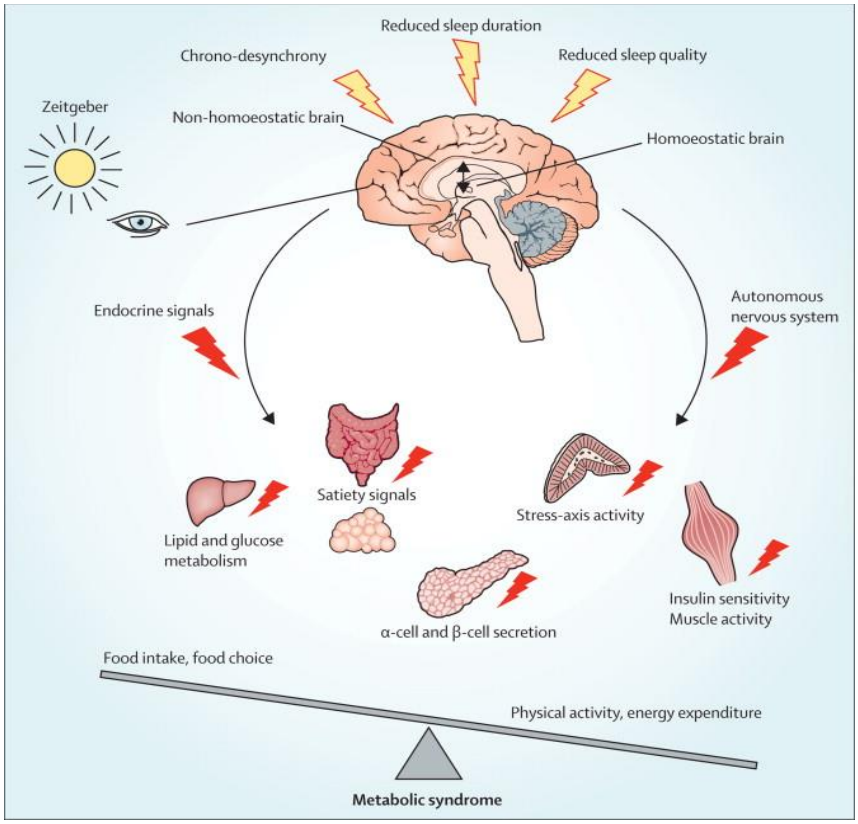

Figure 1. 1 Schematic diagram showing how sleep loss can cause adverse metabolic traits

Reduced sleep duration and sleep quality, and circadian desynchronisation of the sleep–wake cycle (chronodesynchrony) lead via neuroendocrine efferences and modulation of autonomous nervous system activity to increased hepatic glucose production and reduced peripheral glucose uptake (eg, in muscles), changes in pancreatic α-cell and β-cell function, increased stress axis activity (eg, enhanced adrenal cortisol and catecholamine release), and change in secretion of appetite-regulating hormone (eg, ghrelin, leptin) from the gastrointestinal tract and adipose tissue, promoting food intake. These changes in conjunction with a putatively reduced physical activity and energy expenditure, eventually result in positive energy balance and cumulate in adverse metabolic traits, as observed in the metabolic syndrome [15].

Obstructive sleep apnoea (OSA), a common sleep disorder, characterized by pharyngeal collapse, is getting increasing attention because of its neurocognition and cardiovascular sequelae [16]. The prevalence of OSA was estimated to be up to 50% in middle-aged men based on a population-based study between 2009 and 2013 in Switzerland [17]. Despite greater recognition of OSA, a majority of the affected population are undiagnosed [18]. OSA has been suggested to be associated with CVD and metabolic dysregulations (demonstrated in Figure 1.2) [19]. Although the mechanism of OSA is complicated and multifactorial, the activation of inflammatory has been suggested as an important pathophysiological pathway [20].

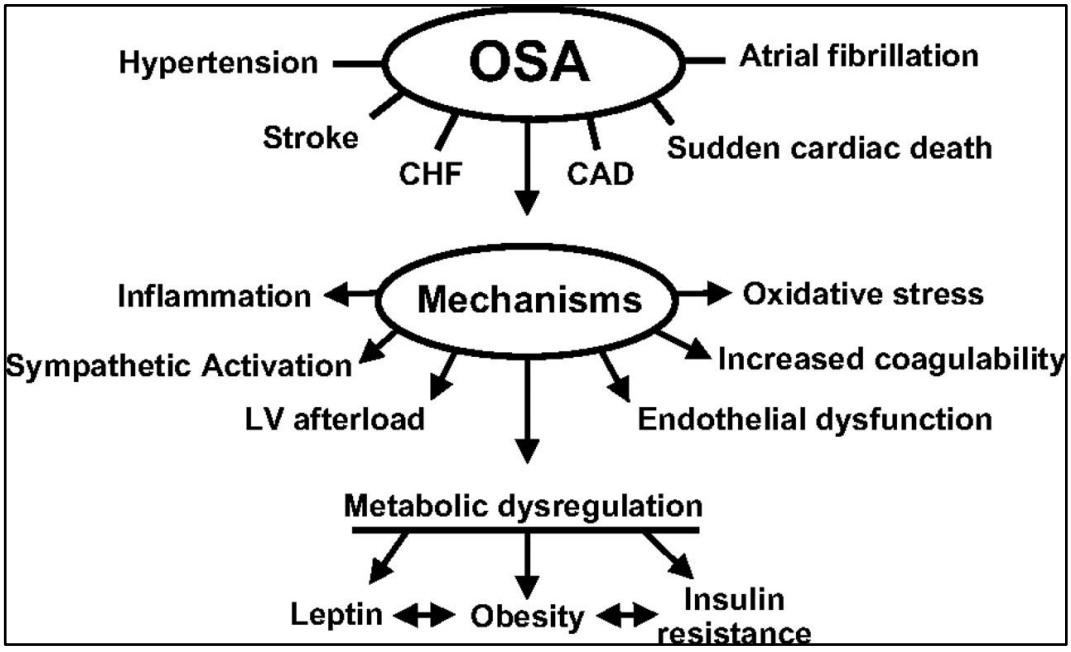

Figure 1. 2 Association between OSA and CVD [19]

Partial list of the disease mechanisms associated with OSA considered as possible links to several CVD and metabolic dysregulation. CHF, congestive heart failure. CAD, coronary artery disease. LV, left ventricular. OSA, obstructive sleep apnoea.

As indicated in Figure 1.1 sleep loss may result in increased food intake, with many studies suggesting that inadequate sleep is associated with increased craving for high density snacks [21] and fatty foods [22] and reduced consumption of fruits and vegetables consumption [23]. On the other hand, evidence suggests that sleep can be affected by dietary factors [24]. This has led to a strong interest in investigating the possible measures to improve sleep, particularly through easily applied dietary preventions. Previous evidence suggested that sleep can be regulated by various hormones that can be induced by food intake through communication between hypothalamus and the brain [24]. Laboratory studies have shown that a diet that is rich in high glycaemic index may help trigger sleep onset [25]; healthy subjects with a high-fat-low-carbohydrate meal felt sleepier than their counterparts [26]; and a fatty meal aggravated apnoea in patients with OSA [27].

1.2 Rationale and framework for research

Existing evidence from laboratory studies supports the impact of diet on sleep, as mentioned above. However, it is unclear whether replication of these findings can be made in community settings at the population level. In addition, the assessment of dietary factors has focused primarily on single nutrients/foods, and there is a lack of research assessing diet as a whole. These are the gaps in the current knowledge.

As diet is a relatively broad concept, this thesis investigates the association between diet and sleep parameters from the following aspects: 1) macronutrients intake; 2) dietary patterns and 3) nutrients patterns. A body of evidence has shown the associations between macronutrients intake and sleep parameters [25, 27-29], and the mechanism has been suggested regarding tryptophan metabolism and changes among circadian, hormonal, central nervous and metabolic systems [30, 31].

It is more likely that foods are taken simultaneously. Therefore, the interactions among foods and nutrients should not be ignored. Dietary pattern analysis can address the possible interactions among foods and nutrients, highlighting the impact of diet in health outcomes [32]. Dietary patterns have been shown to be associated with metabolic syndrome [33], depression [34], stroke [35] and mortality [36] in adults. However, the association between dietary patterns and sleep is not well studied.

Although food-based dietary pattern assessment considers the interaction among foods, a limitation is that dietary patterns may be population (culture and country) specific and influenced by food availability [37]. Nutrient pattern analysis takes into account the interaction among nutrients but provides an easier way to compare between populations because no matter what foods are consumed, the nutrients that are broken down from the foods remains the same [38]. Among the existing studies that investigated nutrient patterns, most of them focused on cancer patients [39-41], one focused on obesity [42], and few have examined the association with inflammation.

A body of evidence has suggested the effect of diet on inflammation [43]. In particular, fibre, ω-3 polyunsaturated fatty acids, fruits and vegetables are anti-inflammatory and saturated fatty acids and trans-fatty acids are pro-inflammatory [44]. As sleep disturbance is associated with a range of metabolic and cardiovascular consequences, as described above, inflammation may contribute to the association between diet and sleep. In conclusion, the framework is conceptualised in Figure 1.3.

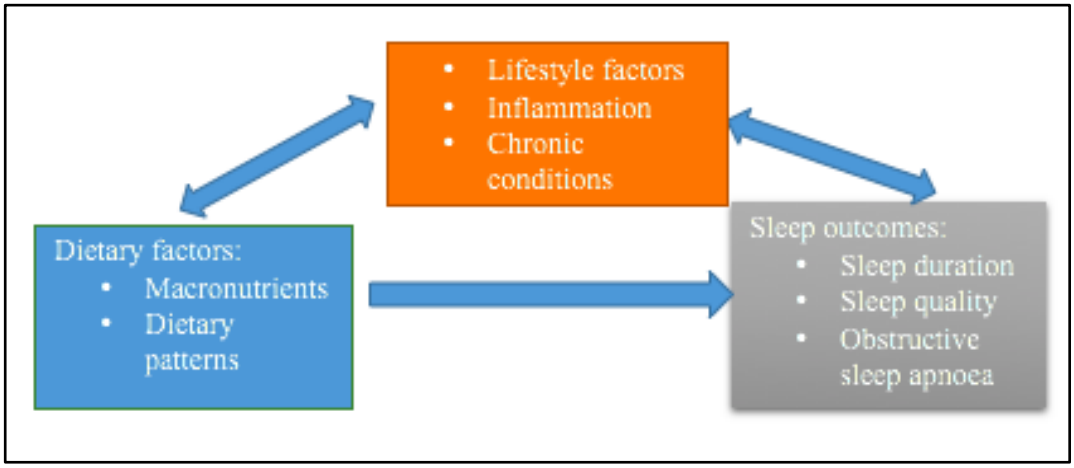

Figure 1. 3 Framework of the association between dietary factors and sleep in this thesis

On the pathway between dietary factors and sleep outcomes, factors including lifestyle factors, inflammation and chronic conditions may moderate/mediate the association.

1.3 Aims and objectives

The aim of this thesis is to explore the association between diet and sleep, as well as other factors including inflammation, lifestyle factors and chronic conditions that could modify such association. In particular, this thesis aims to investigate the associations between comprehensive dietary assessments and sleep outcomes including both subjective and objective measurements in middle-aged and elder Australian men.

The objectives of this thesis include:

- To examine whether macronutrients intake was associated with apnoea-hypopnea index (AHI) and polysomnography (PSG) measured sleep duration and self-reported sleep symptoms.
- To identify dietary patterns and investigate how dietary patterns are associated with PSG measured sleep outcomes as well as self-reported sleep symptoms.

- To examine the association between nutrient patterns and inflammation, and the interactions between nutrients patterns and sleep disorder and lifestyle factors and chronic conditions.

1.4 Format and outlines of thesis

This thesis is by publication, and a combination of written text and peer-reviewed journal papers that have either been published (Chapter 4 and 6) or been accepted for publication (Chapter 5). The format of this thesis is as following:

Chapter 1: Introduction

Chapter 2: Review of literature

Chapter 3: Methods

Chapter 4: Associations between macronutrient intake and obstructive sleep apnoea as well as self-reported sleep symptoms

Chapter 5: Dietary patterns and sleep parameters

Chapter 6: Nutrient patterns and chronic inflammation

Chapter 7: Discussion, future directions and conclusion

References

CHAPTER 2 REVIEW OF LITERATURE

2.1 Sleep duration

Although there are no standard criteria for optimal sleep duration, as it may vary in population and culture, most studies recommended 7-8 hours/day as a normal range of sleep duration [45]. Short sleep therefore may be regarded as less than 7 hours/day although even shorter sleep duration (eg. ≤6 hours/day, ≤5 hours/day and ≤4 hours/day) has been defined in different studies [46-48]. On the other hand, equal or longer than 9 hours/day is regarded as long sleep duration, although again other studies have used even longer duration (eg. ≥10hours/day and ≥12hours/day) [49, 50]. Several studies have demonstrated a U-shaped relationship between sleep duration and type 2 diabetes [51] as well as all-cause mortality [45]. This demonstrates the importance of an optimal sleep duration in health outcomes.

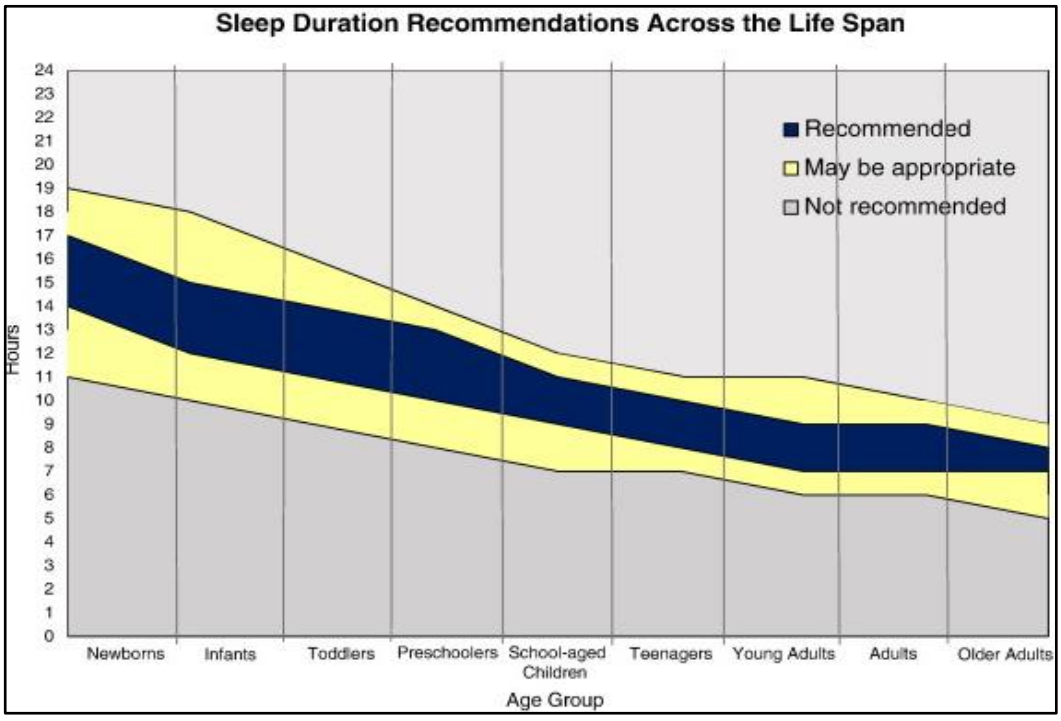

Figure 2. 1 Sleep duration recommendation across the life span, by the American National Sleep Foundation [3]

In 2015, the American National Sleep Foundation along with a multi-disciplinary expert panel issued new recommendations for appropriate sleep duration for different age groups.

The recommended daily sleep duration was 14-17 hours for newborns (0-3 months), 12-15 hours for infants (4-11 months), 11-14 hours for toddlers (1-2 years), 10-13 hours for pre-schoolers (3-5 years), 9-11 hours for school-aged children (6-13 years), 8-10 hours for teenagers (14-17 years), 7-9 hours for young adults (18-25 years) and adults (26-64 years), and 7-8 hours for older adults (65 years and above) (Figure 2.1) [3].

2.2 Sleep quality

Sleep quality, despite its common use, is a term which lacks a standard definition and is mostly inferred from a collection of objective and subjective measurements [52]. Common constructions of sleep quality are likely to be sleep quantity, wakefulness (both prior to and following sleep onset), and feeling of refreshment upon awakening, as well as daytime sleepiness [4]. There are a number of both subjective and objective tools that have been used to measure sleep quality and these tools are often jointly used due to the difficulties in measuring sleep quality through objective fashion only. These measurements include the Epworth Sleepiness Scale (ESS) [53], Pittsburg Sleep Quality Index (PSQI) [54], actigraphy [55], and PSG [56].

Described in Table 2.1 is the detailed information for these instruments.

Table 2. 1 Common sleep quality measures

	Characteristics	Total scoring and interpretation
Subjective measurement		
Epworth Sleepiness Scale (ESS) [53]	The ESS is a subjective measure of daytime sleepiness. The questionnaire contains eight situations in which the participants rate their tendency for daytime sleepiness with a scale ranging from score 0-3. No chance of dozing=0 Slight chance of dozing=1 Moderate chance of dozing=2 High chance of dozing=3	Total score=24 Unlikely to have abnormally sleepiness: 0-7 Average sleepiness: 8-9 Excessive sleepiness: 10-15 Excessive sleepiness and medical attention required: 16-24.
Pittsburg Sleep Quality Index (PSQI) [54]	The PSQI contains 19 self-rated items and 5 questions rated by the bed partner (if available). Only self-rated questions are included in the scoring. The 19 items are combined to form seven 'component' scores, each of which has a range of 0-3 points. • Very good=0 • Fairly good=1 • Fairly bad=2 • Very bad=3	Total score==21 No difficulties: 0 Sleep disturbance: ≥5
Objective measurement		
Actigraphy [55]	Actigraphy is a methodology for recording and analysing activity from small computerized devices worn on the body. Reliability and validity of actigraph measures have been published and a comparable consistency with PSG measure has been indicated.	Sleep statistics for identified sleep intervals are generated by scoring algorithms validated in patients with sleep disorders. The commonly used statistics are sleep time, sleep efficiency, wake after sleep onset, number of wake bouts and sleep onset latency.
Polysomnography (PSG) [56]	PSG is a continuous and simultaneous recording of multiple physiologic variables during sleep, including electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG), respiratory air flow, respiratory effort, pulse oximetry, body position, and snoring.	A score was given by sleep physicians and sleep technicians. The score consists of: sleep onset latency, sleep efficiency, sleep stages, any breathing irregularities, arousals, cardiac rhythm abnormalities, leg movements, body position and oxygen saturation.

2.3 Obstructive Sleep Apnoea

OSA is a condition characterized by repeated episodes of partial or complete collapse of the upper airway during sleep [57]. The severity of OSA was assessed by the number of apnoea and hypopnea per hour during sleep, i.e. AHI. In a review by Franklin *et. al*. summarising data from 11 countries, the prevalence of OSA (AHI≥5) was estimated from 22% in men and 17% in women [58]. Epidemiologic studies have suggested the associations between OSA and a range of morbidities and mortality [59]. The associations between OSA and impaired sleep quality including excessive daytime sleepiness, snoring and waking with a chocking sensation have been indicated [16, 60], although other studies did not find any associations between OSA and excessive daytime sleepiness [61, 62]. Several risk factors have been suggested to be associated with OSA. Cohort studies have shown that the prevalence of OSA increases with age and becomes relatively steady after reaching 60 years of age [63, 64]. OSA is also more common in men than in women in general and clinical populations [65, 66]. Young *et. al*. have reported that 58% of moderate to severe OSA is associated with obesity [67]. Longitudinal studies have shown that the increase of body weight over time can progress the development and severity of OSA [68, 69].

2.4 The association between diet and sleep parameters

2.4.1 Macronutrient intake and sleep

The associations between macronutrient (carbohydrate, protein and fat) intake and sleep including duration and quality have been largely studied, however, with uncertainty. Most studies were cross-sectional, and the rest were controlled laboratory experiments, with no prospective studies. The major studies with detailed information are presented in Table 2.2 and Table 2.3.

Carbohydrate

Laboratory studies found that carbohydrate (high glycaemic index (GI)) was associated with a shortened sleep onset in healthy young men [25] but with increased arousal in children compared with low GI [70]. In cross-sectional studies, carbohydrate particularly from high GI and glycaemic loading (GL=GI*the amount of carbohydrate) was associated with increased sleep duration in toddlers [71]. However, another cross-sectional study in adolescents found that carbohydrate intake was not associated with sleep duration in either gender [72]. In middle-aged non-shift workers, high carbohydrate intake (>50% vs ≤50% of total energy) was associated with difficulty in maintaining sleep among middle-aged workers [29].

It may not be surprising that the associations between carbohydrate and sleep parameters are inconclusive as highlighted by the variety of sugar chains with different metabolisms contained in dietary carbohydrate.

Protein

Similar inconsistency was found in the association between protein intake and sleep. In young children, no association between protein intake and sleep duration was observed [71]. In adults, low protein intake (<10.8% of energy intake vs ≥ 10.8% of energy intake) was associated with poor sleep regularity (odds ratio (OR) 2.1, 95% CI 1.3-3.3) [73] and low intake of protein (<16% of energy intake vs ≥ 16% of energy intake) was associated with poor sleep quality (OR 1.24, 95% CI 1.04-1.48) [29]. However, high protein intake (≥19% of total energy vs <19% of energy intake) was associated with difficulties of maintaining sleep (OR 1.40, 95% CI 1.12-1.76) [29]. A further two studies did not find any association between protein intake and sleep duration/quality [72, 74]. Randomized controlled studies however, suggested that higher protein intake may improve sleep quality among middle-aged overweight/obese adults [75].

Fat

Fat intake within evening meals was associated with longer sleep duration in young German children, although without significance after adjustment for age/sex/maternal age at birth of child [71]. In the study based on the Chinese national survey of nutrition and health in adults [22], although the magnitude is small and the results only reached borderline significance when comparing the highest fat intake and lowest fat intake, the negative trend between fat intake and sleep duration was suggested. For sleep quality, one randomized-cross over study showed that low fibre and high saturated fat and sugar intake was associated with increased arousals in young and middle-aged healthy adults [28]. This is consistent with the result of the NHANES (National Health and Nutrition Examination Survey) study that reported that a low fat/cholesterol diet was associated with lower risk of non-restorative sleep [76]. However, other studies did not find any associations between fat intake and sleep quality [73] or insomnia symptoms [29].

Energy intake

A positive association between energy intake and sleep duration was found in children aged 1.5-2 years [71]. Night caloric intake has been suggested in women but not in men to be positively associated with sleep latency and negatively associated with sleep efficiency [74]. Other studies [22, 73] did not find any association between energy intake/expenditure and sleep duration/quality.

Table 2. 2 Characteristics of studies that investigated the associations between macronutrient intake and sleep (cross-sectional studies)

First author, year, country	Sample size	Subjects characteristics	Macronutrients/energy assessment	Sleep (duration or quality) assessment	Adjusted variables	Main findings
Yamaguchi *et. al.* [73], 2013, Japan	1368	35-69 years old non-shift workers	Validated short food frequency questionnaire (FFQ) (Tokudome Y, 2005; Goto C, 2006; Imaeda N, 2007)	Self-administered questionnaire	Age, sex, body mass index (BMI), stress level, current smoking/alcohol, physical activity	Sleep quality (self-reported) - Carbohydrate intake: Quartile 4 (≥vs 70.7% of total energy) had a risk of poor sleep-wake regularity than Quartile 2 (60.1-66% of total energy); Protein intake: Quartile 1 (<10.8 of total energy) had a risk of poor sleep-wake regularity than Quartile 2 (10.8-11.8% of total energy); Fat intake: did not differ in good and poor sleep reporter. Energy intake: did not affect sleep quality
Tanaka *et. al*. [29], 2013, Japan	4435	Non-shift workers	Brief-type self-administered diet history questionnaire (BDHQ) (Sasaki S, 1998; Kobayashi S, 2012)	Self-reported difficulty in initiating sleep (DIS), difficulty in maintaining of sleep (DMS), poor quality of sleep (PQS)	BMI, mental well-being, alcohol intake, coffee drink habits, medical history of chronic disease eg. hypertension, hyperlipidemia, diabetes, angina, myocardial infarction, stroke	Sleep quality (self-reported) – Carbohydrate intake: high intake (<50% vs ≥50% of total energy) was associated with DMS; Protein intake: low protein intake (<16% vs ≥16% of total energy) associated with DIS and PQS; high protein intake (>19% vs ≤19% of total energy) associated with DMS; Fat intake: was not associated with none of insomnia

						symptoms (DIS, DMS, PQS); Energy intake: NA
Awad *et. al.* [72], 2012, USA	319	Caucasian and Hispanic children aged 10-17 years	Self-administered Rockett Youth/Adolescent questionnaire (Rockett HR, 1995; Rockett HR, 2003)	Polysomnography (PSG)	Age, BMI	Sleep duration – Carbohydrate intake: was not associated with sleep duration in either gender Protein intake: was not associated with sleep duration in mixed or either gender; Fat intake: was not associated with sleep duration in mixed nor either gender; Energy intake: NA; Others: No association between carbohydrate, protein, fat and sleep stages and rapid eye movement (REM) percentage in mixed genders. In girls, total fat intake correlated with REM sleep; In boys, total fat intake correlated with REM sleep when controlling age and BMI percentile
Diethelm *et. al.* [71], 2011 Germany	594	Term singletons with birth weight>2.5kg, at age 1.5 and 2 years	3-days weighed dietary records evening meal (17:00-21:00 within 1 hour and total caloric intake≥10kcal), LEBTAB database	Question 'How many hours does your child usually sleep per 24h?'	Duration of full breastfeeding, parental education, smoking in the household, rapid weight gain	Sleep duration- Carbohydrate intake (g): particularly from high glycaemic index (GI) was associated with longer sleep duration; higher glycaemic loading (GL) associated with longer sleep duration; Protein intake: was no associated with sleep duration; Fat intake: was no

						associated with sleep duration; Energy intake: was positively associated with energy intake
Crispim *et. al.* [74], 2011, Brazil	52	Healthy 27 women and 25 men aged 19-45 years	Self-administered food diary for non - consecutive 3 days Nutwin 1.5 software (caloric and macronutrient)	PSG	Age, gender, BMI, socioeconomic status	Sleep quality (PSG measured) – Carbohydrate intake (g): was not associated with sleep efficiency; Protein intake (g): was not associated with sleep efficiency; Fat intake (g): was negatively associated with sleep efficiency and REM, and was positively associated with REM latency; Energy intake: in women but not in men: caloric intake (night intake) positively associated with sleep latency; negatively associated with sleep efficiency; Sleep duration- No association of nocturnal intake (carbohydrate, protein, fat, calories) with sleep duration
Shi *et. al*. [22], 2008, China	2828	Adults	Food weighing, 3-day food records (Chinese food composition table, 2005)	Asked by 'how many hours you slept every day', and recorded into 3 categories: 7-9h/day, ≤7h/day, ≥9h/day	Age, gender, income, education, residence, occupation, smoking and alcohol drinking	Sleep duration- Carbohydrate intake: NA; Protein intake: NA; Fat intake: Negatively associated with sleep duration (quartile 4 vs quartile 1); Energy intake: Energy intake was not associated with sleep duration.

Grandner *et. al.* [76], 2014, USA	4552	Aged 18+ years, subjects from NHANES	24-hour recall	Questionnaire assessed (difficulty falling asleep and maintaining sleep, non-restorative sleep and daytime sleepiness)	Age, sex, race/ethnicity, education, household income exercise and BMI .	Sleep duration- NA Sleep quality- Low fat/cholesterol diet was associated with less non-restorative sleep and daytime sleepiness. None effects of other macronutrients on other sleep symptoms.
Grandner *et. al.* [77], 2010, USA	459	Postmenopausal women, aged 50-81 years	FFQ	Sleep dairies and actigraphy	Age, education, income, BMI, physical activity and daily grams of food consumption	Sleep duration- (actigraphy measured) was negatively associated with total fat intake and caloric intake Sleep quality (subjective napping)- negatively associated with total fat intake, caloric intake

NHANES, National Health and Nutrition Examination Survey.

Table 2. 3 Characteristics of studies that investigated the associations between macronutrient intake and sleep (controlled laboratory experiments)

First author, year, country	Sample size	Subject characteristics	Macronutrients/energy assessment	Intervention	Sleep (duration or quality) assessment	Exclusion criteria	Main findings
Nehme *et. al.* [78], 2014 Brazil	51 (phase 1), 24 (phase 2, intervention)	Male night security guards	Phase 1: 24-hour recall, Phase 2: baseline (24 - hour recall)	Phase 2: 3 consecutive weeks: w1, baseline; w2, carbohydrate condition (20-30% higher than baseline); w3, protein condition (30-40% higher) (3 conditions were within subject cross over)	Actigraph (Ambulatory Monitoring, Ardsley, NY); Karolinska sleep scale (KSS) (Akerstedt & Gillberg, 1990)	Working night shift <6 months, medication that may cause sleep problems, hormonal or mental illness, holding second jobs, sleep disorder, drug users	Sleep duration- Carbohydrate: No difference of sleep duration after increasing carbohydrate-rich in night meal; Sleepiness- No difference after increasing carbohydrate rich in night meal
Afaghi *et. al.* [25], 2007, Australia	12	Healthy aged 18-35 years old men normal weight	High glycaemic index (GI=109), low GI (50)	Randomised 3 conditions: high GI meal 4 h before bedtime; high GI meal 1h before bedtime; low GI meal 4 h before bedtime (3 conditions were within subject cross over)	Polysomnography (PSG) (C3/A2, O2/A1); VAS sleepiness scale	Current or past history of significant medical, psychiatric, or sleep disorders, medication (sedatives or antidepressants), regular alcohol intake >20g/da	Sleep duration- Carbohydrate: High GI vs low GI (4 hours before bedtime): More reduction in sleep onset latency (SOL); No difference in total sleep duration

						y, exercised vigorously 24 hours before the sleep study	Sleepiness- High GI 4 hours vs 1hour before bed felt more sleepier
Driver. [79], 1999 *et. al.*, South Africa	7	Men aged 20-24 years, mean BMI 23.4±2.6	Prepared manipulated meals, bomb calorimetry, software package Foodfundi	Randomised 3 meal treatments: no meal (fast), control meal, high-energy meal	electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG) (Medelec DG20. Vickers Medical, Surrey, UK)	Not known	Short term energy modified evening meal did not affect sleep duration nor sleep quality (PSG measured)

Compared with sleep duration and sleep quality, the associations between macronutrient intake and OSA are relatively less studied. A fatty meal (70% vs 18% of total energy) was associated with increased sleep apnoea in patients with OSA in the laboratory setting (n=19) [27]. A randomized trial found that an energy-restricted diet (800 kcal/day reduction of baseline total energy intake) was associated with a reduction of AHI compared with the controls in obese patients (n=21) [80].

2.4.2 Individual food intake and sleep

The associations between individual foods and sleep have been investigated. For example, coffee, widely consumed around the world, is used to mitigate sleepiness and enhance performance. The association between caffeine and sleep has been debated. Children who drank caffeinated beverages (30% of the study population) had 15 fewer minutes of sleep per night than did children who did not drink such beverages as reported in an American study (n=625) [81], suggesting the negative effect of caffeine on sleep duration. However, another study did not find an association between coffee consumption and decreased sleep duration in middle-aged adults (n=1498) [82]. A recently published systematic review of epidemiological studies and randomized controlled trials based on a total of 58 studies found the deleterious effects of coffee and caffeine on sleep [83]. These effects included prolonged sleep latency, reduced total time and sleep efficiency, and poor perceived sleep quality. In addition, they found that older adults may be more sensitive to coffee and caffeine compared with younger adults.

Another popular individual food that has been linked to sleep is cow's milk. It has been considered a traditional sleep-improving food worldwide [24]. As early as 40 years ago, a study using electrophysiological recordings showed improvement in sleep duration and reduction in unnecessary awakenings in adults who had milk with Horlicks powder, a

malted barley and wheat product [31]. However, studies on elderly people with usual or larger doses showed no effect of normal commercial milk on sleep (n=70) [84]. In the same study, when the normal commercial milk was replaced with melatonin enriched milk in the same elderly subjects, better sleep and rest in the previous night was reported. This indicated that the key element of sleep improvement effect of milk is melatonin, which is a natural component in cow's milk. The lack of melatonin might explain why commercial milk has a weak or no effect on sleep.

In a randomised double blind placebo controlled crossover trial among 20 healthy volunteers found an elevated total melatonin content was significant higher in the tart cherry juice group, suggesting a beneficial effect in improving sleep duration and quality [85].

A intervention of kiwifruit consumption one hour before bed for four weeks in 22 volunteers showed significantly improved sleep quality assessed by PSQI and actigraphy [86].

2.4.3 Dietary patterns and sleep

While numerous research has been focusing on certain nutrients/foods, increasing interest has been raised in the patterns of food intake, given that foods are more likely to be taken simultaneously. Dietary patterns have been shown to be associated with metabolic syndrome [33], depression [34], stroke [35] and mortality [36] in adults. However, the association between dietary patterns and sleep is not well studied.

Currently, only two studies have assessed the association between dietary patterns and subjective measured sleep. The first study was conducted among 1976 Portuguese children, aiming to examine the association between dietary patterns and gender, parental education, physical activity, sleep duration and obesity [87]. Dietary intake was assessed by food frequency questionnaire (FFQ), and sleep duration was asked and coded into three

categories: <8hours/day, 9hours/day and ≥10hours/day. Dietary pattern rich in fruits and vegetables was positively associated with those reported sleep ≥10 hours/day (β=0.099, p=0.026). The second study was conducted in Japanese adults. A dietary pattern characterized by vegetables, mushrooms, potatoes, seaweeds and soy products was associated with a decreased risk of difficulty initiating sleep among 2025 Japanese adults (OR 0.75 (95% CI 0.57, 0.99)) [88]. Dietary intake was assessed by a validated, brief, self-administered diet-history questionnaire and sleep symptoms were assessed based on relevant questions asked about difficulty in initiating sleep and restorative sleep.

2.4.4 Nutrient patterns and sleep/inflammation

The association between dietary patterns and inflammation has been largely studied, but no studies have connected the association with sleep disorders, which are linked with a range of chronic diseases and inflammation. Nutrient pattern analysis, as an alternative of dietary pattern analysis, with advantages for comparisons between populations [38], has emerged in the nutritional epidemiological studies. However, no available data of the association between nutrient patterns and sleep or inflammation exists.

2.4.5 Possible mechanisms of the associations between diet and sleep parameters

There are several possible mechanisms that may explain the associations between diet and sleep parameters. From the nutrients perspective, the influence on sleep seems to be via the tryptophan-serotonin-melatonin synthesis, so that the serotonergic neurons innervate brain regions and further intermediate the production of melatonin to regulate sleep [24]. Tryptophan is a precursor to the neurotransmitter serotonin and the neurosecretory hormone melatonin, which are both linked to sleep and alertness [89]. The tryptophan comes from dietary protein that can facilitate catecholamine synthesis, however, plasma tryptophan

concentration is also affected by dietary carbohydrates. Dietary carbohydrates and protein can both affect tryptophan metabolism through the availability of tryptophan uptake into the brain via the blood brain barrier [31].

In addition, the interactions between nutrients digested and release of various gut hormones that communicate with the hypothalamus and the brain seems to be another mechanism. For example, long-term high fat intake can lead to elevated levels of leptin and decreased levels of ghrelin [90]. In addition, metabolic cues including leptin, glucose and ghrelin can in turn regulate arousal, wakefulness and feeding via orexin, the neuropeptide produced in hypothalamic neurons [91]. Lack of orexin has been shown to be related to narcolepsy [92]. In the lateral hypothalamic area, leptin responsive neurons can inhibit orexin neurons and lead to sleepiness [93].

Other possible mechanisms including bioactive peptides and non-protein nitrogen fraction of diet that are released after enzymatic digestion and enter peripheral blood and exert systemic effects [24].

2.5 Other factors that are associated with sleep parameters

2.5.1 Inflammatory markers

Inflammatory markers have also been suggested to increase sleep difficulties. High C-reaction protein (CRP) levels was associated with short sleep duration measured by PSG [94], although only in women (n=340). Interleukin-1 (IL-1), Interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) may also be associated with sleep regulation [95]. Patients (n=11) with insomnia have been shown to have higher circulating levels of IL-6 than normal sleepers in a pilot study [96]. An increase in levels of inflammatory markers including CRP,

TNF-α and IL-6 were found to be higher in OSA patients compared to controls in a meta-analysis [97]. These findings all support the link between inflammations and sleep disorders.

2.5.2 Chronic diseases

As stated in Chapter 1, sleep disorders have been associated with a range of chronic diseases, and vice versa, chronic diseases may also cause sleep problems. For example, Foster *et. al.* have previously demonstrated a higher prevalence of OSA (86%) in patients with type 2 diabetes [98]. In a cross-sectional study of 137 extremely obese patients, 33% had OSA among the normal glucose tolerance group, while a significant higher percentage of OSA (78%) was found among patients with pre-diabetes and diabetes [99]. This may be due to insulin resistance, as high baseline insulin levels have been associated with six-year incident of OSA among 1780 men and 1785 women [100]. Excessive weight gain or obesity has been regarded as the major risk factor for sleep disorders. A 10% weight gain compared to a stable weight predicated about 32% increase in AHI and a six times increase in the risk of moderate to severe OSA in a four year prospective study from the Wisconsin Sleep Cohort Study [68]. This may be explained by the extra fat distribution around the upper airway that leads to airway collapse. As demonstrated in a randomised one-year intervention study (n=36), more adipose tissue in the pharynx were observed in OSA patients compared with controls [101].

2.5.3 Lifestyle factors and social environmental factors

Lifestyle is a broad concept, which may include any type of life patterns. Main lifestyle factors that relate to health outcomes include smoking, alcohol consumption, and physical activity. A higher level of lifestyle regularity (including getting out of the bed, first contact with another person, starting work, housework or volunteer activities, having dinner and going to bed) reported fewer sleep problems compared with low levels of lifestyle regularity

among 100 healthy subjects [102]. Smoking or alcohol drinking did not differ significantly between those with or without adequate sleep in another Japanese study among workers over 6-year period (n=2000) [103]. However, sleep difficulties including less total sleep time, longer sleep onset, increased difficulty falling asleep, maintaining sleep, and waking up earlier than desired have been reported among current smokers compared to never smokers in a large population study from the American National Health and Nutrition Examination Survey (n=4973) [104].

The impact of alcohol consumption on sleep dates back to early sleep experiments conducted by Nathaniel Kleitman in 1939, who had observed the effects of ethanol given 60 minutes before bedtime on body temperature and motility during sleep in healthy normal non-drinkers [105]. Extensive research has since been conducted on the effect of ethanol on sleep. In healthy subjects (n=6), low dose (0.16g/kg body weight, 0.32g/kg body weight) of alcohol consumption before bed increased sleep efficiency, but the sleep-promoting benefits dissipated at moderate or higher alcohol doses (0.64g/kg) [106]. A population perspective study from the American National Health and Nutrition Examination Survey explored the association between subjective sleepiness and alcohol consumption and sleep duration (n=2919) [107]. They found an interaction between increased heavy drinking frequency and decreased sleep duration predicting increased risk of daytime sleepiness.

Exercise or physical activity has been recommended by the American Sleep Disorder Association as a non-pharmacological intervention to improve sleep [108]. A body of studies have suggested the beneficial effects of physical activity on sleep; however, how large these benefits could be and how much the benefits are affected by other moderators such as age, and the type and duration of the physical activity still remain unclear [109]. Kredlow *et. al* [110] have conducted a meta-analysis to examine the effects of acute and

regular exercise on a range of sleep variables and explore the potential factors that may moderate the effects. Acute exercise has small beneficial effects on total sleep time, sleep onset latency and sleep efficiency and slow wave sleep and rapid eye movement (REM) sleep, and moderate benefits on wake after sleep onset (WASO) [111, 112]. For regular exercise, most studies suggested a small beneficial effect on total sleep time and sleep efficiency, and sleep onset latency, but a moderate to large benefit on sleep quality [113, 114]. Moderator analyses have also been conducted in the meta-analysis, suggesting the effects of exercise can be moderated by factors including sex, age, exercise type, duration and adherence but not the intensity [110]. For example, for every 10% increase in the percentage of the female sample, the effect size of the acute exercise on WASO was reduced by 0.05 standard deviation units. A 10-year increase in the mean age of the sample was associated with a 0.15 standard deviation unit decrease in the beneficial effects of reducing sleep onset latency (SOL).

Apart from the behavioural influences on sleep, psychosocial factors are also important in sleep regulation. In a cultural comparison study between the United Kingdom (UK) (n=6472) and USA (n=3027), unmarried subjects were associated with shorter sleep duration and more sleep problems compared with married counterparts [115]. A 36-year Swedish cohort study on two age groups (38 years, n=353 and 50 years, n=380) found lower satisfaction in economic status, social, family was associated with perceived sleep problems in middle-aged women [116]. Similarly, subjects with higher socioeconomic status (SES) reported better sleep compared with those with low SES in a cross-sectional German study among 3281 adults. Factors such as anxiety and depression moderated such association [117].

2.5.4 Shift work

Shift work, is a type of work that takes place on a schedule outside the traditional 9am-5pm period. Shift work has been of interest recently in research due to its impact on health by disturbing circadian rhythms and affecting sleep quality [118-120]. In Australia, about 1.5 million people are shift workers, and the major immediate consequences have been suggested to be impaired alertness, reaction time, and attention maintenance [121]. In total, 32% of night workers and 10% of day workers were estimated to have shift work disorders (i.e. characterized by excessive sleepiness and insomnia due to unfavourable work hours), which have been associated with shorter sleep duration when compared with day workers without shift work disorders [122]. In a Chinese cohort study of assessing the effect of shift work in retired shift workers, shift work was found to be associated with poor sleep quality, hypertension and diabetes, although such association gradually reduced as the time of leaving shift work increased in duration [123].

Melatonin levels of shift workers during night work and daytime sleep were significantly lower, compared with daytime workers [124]. Night shift workers have also been suggested to have greater response of postprandial glucose, insulin and triacylglycerol compared with normal daytime workers [125]. Sheer *et.al.* have conducted a 10-day forced desynchronized protocol to induce circadian misalignment in 10 adults, and they observed a decrease of leptin levels, and an increase of glucose and insulin and mean arterial pressure [126]. This demonstrates the adverse impact of circadian misalignment on cardio metabolic functions and explains its further contribution to the development of obesity and diabetes.

2.6 Summary and gaps in the current literature

In conclusion, the review of the literature has identified a number of issues in the current literature that limits the understanding of the associations between dietary factors and sleep. What is known from the current literature is:

- Sleep deprivations and poor sleep quality have adverse health influence, which is can be linked with diet.
- Dietary factors including single nutrient/food can affect sleep.
- The association between dietary factors and sleep may be explained by interactions between nutrients and gut neuro hormones.

However, what is unclear is:

- What is the association between dietary factors and sleep parameters at the population level?
- How is diet as a whole (dietary patterns) associated with sleep?
- How is diet as a whole (nutrient patterns) associated with sleep?
- Is there an interaction between lifestyle factors and chronic inflammation in relation to sleep?

Given the gap in the current literature, this thesis was designed to answer these questions and contribute to a better understanding of the association between diet and sleep.

CHAPTER 3 METHODS

3.1 Overview of the dataset

CVD and type 2 diabetes are among the leading causes of death globally, including Australia [127]. There is disproportion in the burden of CVD which is higher in men than women across most regions globally. This could be explained by gender-specific behavioural and biological risk factors including the higher prevalence of smoking, inactivity and obesity in men [128]. However, there is a lack of high quality prospective cohort studies that address adequate multiple risk factors particularly in men. In 2009, the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study was established to investigate cardio metabolic diseases risk factors in relation to sex steroids, inflammation, environmental and psychosocial factors in men [129].

The MAILES study is a collaboration between The University of Adelaide, University of South Australia, The Queen Elizabeth Hospital (Woodville, South Australia), The Lyell McEwin Hospital (Elizabeth Vale), and the South Australian Health Department (SA Health). The study involves investigators from a range of disciplines including academic and clinical medicine, public health, epidemiology, social science and nursing, using both quantitative and qualitative research methodologies. The study was supported by the National Health and Medical Research Council of Australia (grant number 627227). Ethics approval was obtained from the Queen Elizabeth Hospital Human Ethics Committee (number 2010054) and the Royal Adelaide Hospital Human Research Ethics Committee (number 020305h).

The broad aim of MAILES is to determine the best set of explanatory variables for development of type 2 diabetes and CVD, which may further help policy makers and researchers in planning of treatment and preventive measures for these diseases.

3.2 Sampling and measures of MAILES

The MAILES study contains 2563 community dwelling men aged 35-80 years old from Adelaide at baseline (MAILES stage 1) from the combination of two population cohort studies: all participants from the Florey Adelaide Male Ageing Study (FAMAS) (2002-2005) [130] and eligible male participants from the North West Adelaide Health Study (NWHAS) (2004-2006) [131]. The MAILES stage 2 (2007-2010) was an approximately five-year follow up consisting of a Computer Assisted Telephone Interview (CATI), questionnaires and biomedical examinations. In total, 1815 men completed the dietary intake during stage 2. The cohort size is sufficient to address the research questions of interest by meeting the following criteria: 1) sample power of 80%; 2) use of a two-tailed test; 3) a 5% chance of type 1 error; and 4) an estimated risk-factor prevalence of 30% (conservative estimate for behavioural risk factors (e.g. physical inactivity).

Participants were recruited using the telephone to conduct interviews with the Electronic White Pages as the sampling frame. Residential households were selected at random by a computer and randomly selection was also conducted within the household for both cohorts for interview and clinic visits [132, 133]. This method of randomly selecting within the household avoids selection bias towards unemployed and retired or housewives, as those most likely to be at home when the initial call was made [134]. The general inclusion criterion were: 1) male and aged 35-80 years at the time of recruitment; and 2) household with a telephone connected and telephone number listed in the Electronic White Pages. The exclusion criteria were: 1) non-English speaking; 2) mental or physical illness that disables the communication ability; 3) too ill or otherwise incapacitated to attend clinics; and 4) current residence in an aged care facility.

From 2010-2012, a further CATI was conducted that including sleep-related questions (n=1629) and a sub-sleep study was performed. In total, 184 participants who had previous diagnosis of OSA were excluded from the sleep study. The rest (1445 men) who reported no previous diagnosis of OSA were further asked if they wished to participate in the sleep study (PSG) (75.2% agreed). A random sample of 1087 was then selected for inclusion with a final 857 men having home based PSG. After repeated measures for initial failed participants (remeasured) and excluding the final invalid cases, 837 participants had valid PSG results, and of them 784 had complete dietary information. The composition of participants at each stage of the MAILES study in terms of the proportion of participants from FAMAS and NWHAS is presented in Figure 3.1. Among those losses to follow-up between MAILES 1 and MAILES 2 (n=525), 99 died, 39 were too ill to participate, 141 withdrew completely before continuing MAILES 2, 77 were unable to be tracked due to loss of contact details and 169 refused to continue due to personal reasons [129]. For the purpose of the thesis, a flow chart showing information regarding dietary and sleep measurement as well as biomarkers is presented in Figure 3.2.

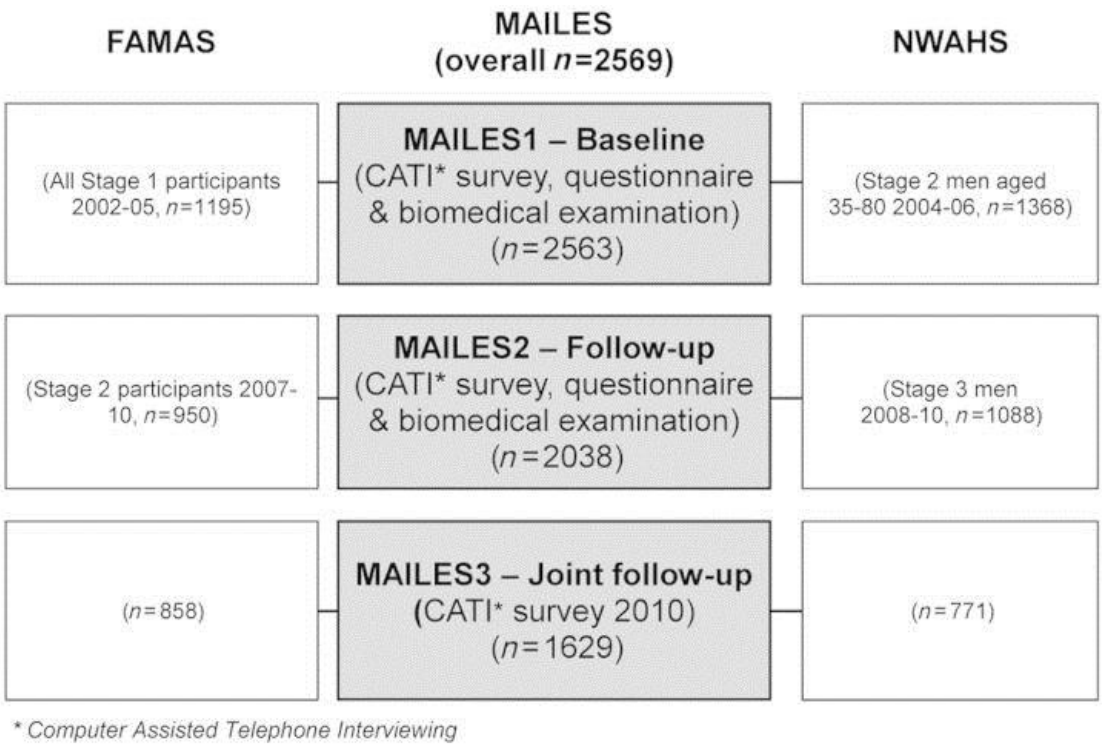

Figure 3. 1 Composition of the study sample at each stage of the MAILES Study, with the numbers of participants drawn from the respective stages of FAMAS and NWAHS [129]

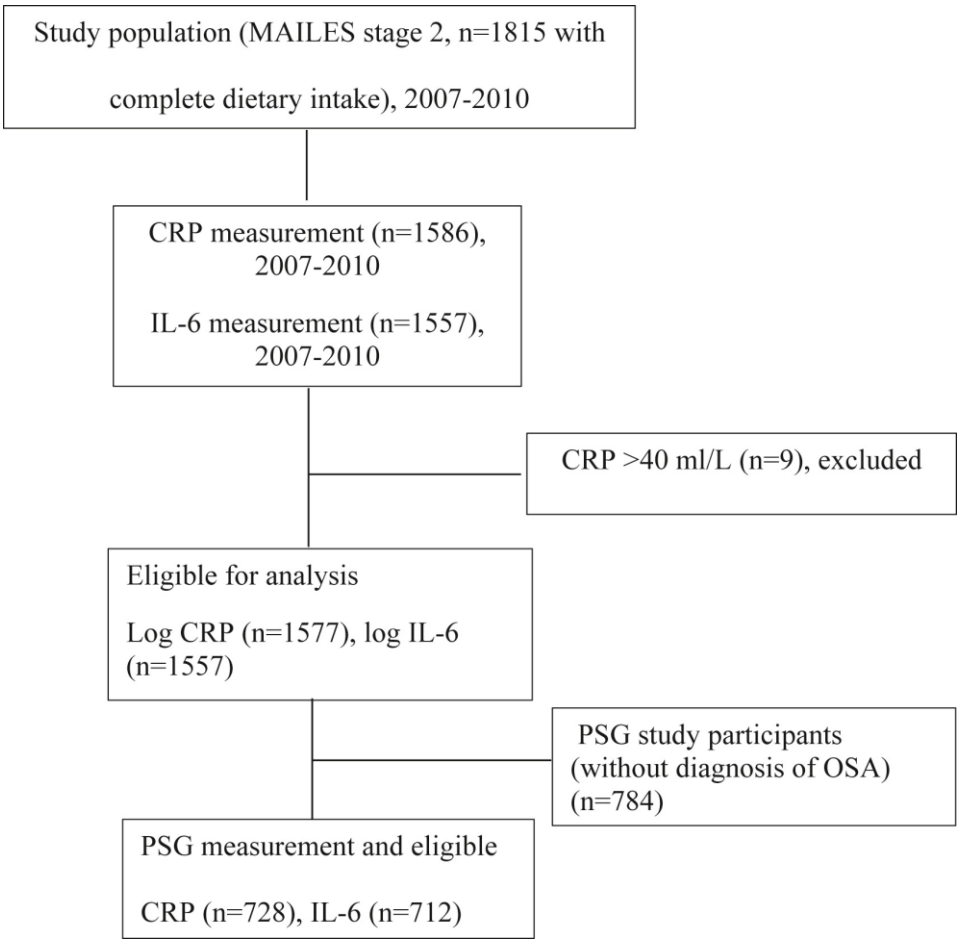

Figure 3. 2 Flowchart of the sample included in the analysis in the thesis

3.3 Variable measurements

For the purpose of the thesis, in addition to the demographic factors, social and psychological factors and lifestyle factors, we focused on dietary factors, sleep factors and biomarkers. The detailed measures are described below.

3.3.1 Dietary factors

Dietary intake was measured using the Cancer Council Victoria Diet Questionnaire for Epidemiological Studies (DQES-V3.1 (food frequency questionnaire (FFQ)). The FFQ has been validated in an Australian population and is widely used in epidemiological studies [135]. The questionnaire asks the participant's habitual consumption of 167 food items and six alcohol beverages over the last 12-month on a 10-point frequency scale. Additional questions were asked about the type of breads, dairy products and fat spreads used. By using the estimated portion sizes and frequencies, the intake of each food was converted to daily equivalents for analyses. Nutrients intakes were computed from the dietary data by the means of the nutrient composition tables in the NUTTAB95 database (Food Standards Australia New Zealand, Canberra, 1995).

3.3.2 Sleep measurements

Sleep measurements consisted of subjective (CATI and self-reported questionnaires) and objective (in-home PSG) approaches. CATI asked general questions regarding sleepiness 'Do you feel sleepy when sitting quietly during the day or early evening?' with three options 1) yes 2) no and 3) sometimes; regarding the awakenings during the night 'Do you feel that you wake, or are woken, frequently during the night?' with three options 1) yes 2) no and 3) sometimes. CATI also asked questions regarding the time of falling asleep and waking up during working days. Also, as mentioned above, CATI also screened out the eligible

participants for the sub-sleep study by asking the question ‘Have you ever been diagnosed with obstructive sleep apnoea with a sleep study?’.

Self-reported sleep data was obtained using the questionnaire including: 1) the STOP (snore, tiredness during daytime, observed apnoea and high blood pressure) questions [136]; 2) the PSQI (total score ranged from 0-21, a score >5 indicates poor sleep quality) [54]; and 3) Epworth sleepiness scale (a 4-piont scale (0-3) on 8 questions regarding dozing off) to assess daytime sleepiness [53].

Objective sleep measurements were obtained from PSG among those without previous diagnosis of OSA. A single overnight 8-channel in-home PSG with Emblettas X100 portable sleep device (http://www.embla.com/index.cfm/id/57/Embletta-X100/) was conducted by an experienced sleep technician according to the current American Academy of Sleep Medicine (alternate) criteria [137]. The PSG monitors many body functions including EEG, EOG, EMG and ECG during sleep. Breathing functions, respiratory airflow and respiratory effort indicators were added along with peripheral pulse oximetry. AHI was computed as the sum of respiratory events (apnoea and hypopnoea) divided by hours slept. AHI severity was categorised as follows: <5/hour, 5-19/hour and ≥20/hour.

3.3.3 Anthropometric measures and blood pressure

Body weight was measured in light indoor clothing without shoes to the nearest 100 grams. Height was measured without shoes to the nearest mm using a stadiometer. Waist circumference was measured to the nearest millimetre midway between the inferior margin of the last rib and the crest of the ilium, in the mid-axillary line in a horizontal plane. Blood pressure was measured twice by mercury sphygmomanometer on the right upper arm of the subject, who was seated and relaxed for five minutes before the measurement.

3.3.4 Biomarkers

Fasting blood samples were drawn during morning clinic visits at MAILES stage 2 assessment in hospital-based clinics (The Queen Elizabeth Hospital and Lyell McEwin Health Service). The participants were re-scheduled if they felt unwell. Blood samples were stored on ice 0.5-3.5 hours before being transported for immediate laboratory analysis. Plasma and sera from blood samples were frozen at -70 °C and thawed for subsequent analysis of inflammatory markers [132]. Serum levels of high-sensitivity CRP and IL-6 were quantitated with an enzyme linked immunosorbent assay (ELISA) and Cobas auto analyser (Roche Diagnostics, Florham Park, New Jersey, US). The inter-assay coefficients of variation were 2.1 for high-sensitivity CRP and 7.8 for IL-6 [129].

Other biomarkers such as insulin (Abbott Architect immunoassay analyser (Abbott Park, IL USA)), glucose (Olympus AU5400 (Olympus Optical C Lid, Japan)), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (Olympus AU5400 (Olympus Optical C Lid, Japan)) were also measured.

3.3.5 Lifestyle factors

Levels of physical activity, smoking and alcohol consumption have also been determined across each stage. The physical activity questions from the Australian National Health Surveys were used to classify participants as sedentary, or having low, moderate or high levels of physical activity [138]. Smoking behaviour (current smoking, pack years) was assessed using the questions adopted from the National Health Survey and alcohol consumption (how often do you drink and how many standard drinks per day on average week) was assessed according to the Australian National Health and Medical Research Council [139] .

3.3.6 Chronic conditions and medication

Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L or with previous diagnosis of diabetes or on medication for diabetes. Depression was determined by the Centre of Epidemiological Studies-Depression Scale instrument (score ≥ 16) in NWAHS [140] and the Beck Depression Inventory instrument (score ≥ 10) in FAMAS [141]. Medication use was obtained from Medicare Australia by confidential record linkage, classified according to the Anatomical Therapeutic Chemical (ATC) Classification.

3.3.7 Others

Demographic information including age, marital status, and other risk factors including family history for chronic diseases, social factors including education, household income and work status were also collected via questionnaires.

3.4 Statistical analyses

3.4.1 Associations assessments

Linear regression

Linear regression models the relationship between one or more explanatory variables (X) and the dependent (response) variable Y by fitting a linear equation in the observed data [142]. We applied linear regression to assess the association between dietary patterns and sleep parameters (Chapter 5).

Multinominal logistic regression

Multinomial logistic regression (MLR) is a classification method that generalizes logistic regression to multiclass problems with more than two possible discrete outcomes [143]. The

MLR model is used to predict the probability of category membership on a dependent variables based on multiple independent variables, using maximum likelihood estimation [144].

In the first research of the thesis (Chapter 4), we used MLR to predict the probability of categories of AHI according to the dependent variable of macronutrient intake.

Logistic regression and Poisson regression

Logistic regression models the association between binary responses and one or more independent variables and present the results with OR. However, for any dependent variable with prevalence of more than 10%, prevalence ratios were used rather than OR, as in these circumstances OR may underestimate or overestimate the associations between the exposure and outcome. We used Poisson regression models when the prevalence of the outcome was more than 10%. Poisson regression provides an alternative analysis for better estimates with binary outcomes in cross-sectional studies [145, 146]. Either logistic or Poisson regression models were applied to examine the association between dietary factors and self-reported sleep outcomes through all studies included in this thesis.

3.4.2 Model building

In order to adjust for potential confounding factors of the associations between dietary factors and sleep/inflammation, different models were built for each study. These models include demographic factors, lifestyle factors and chronic conditions and medication, with slight differences in each of the studies included in this thesis. In general, model 1 adjusted for age, model 2 further adjusted for education, smoking, alcohol intake, physical activity and shift-work. Model 3 further adjusted for waist circumference and/or diabetes, depression and medication. Energy intake was further adjusted in model 4 in the study in

Chapter 4. In the study in Chapter 6, chronic diseases related bio-markers including fasting glucose, LDL cholesterol, HDL cholesterol and systolic blood pressure were further adjusted in addition to the demographic and lifestyle factors.

3.4.3 Factor analysis

Factor analysis is a statistical method used to remove redundancy from a set of observed and correlated variables, and define the latent variables i.e. factors. There are two types of factor analysis, where confirmatory factor analysis is used for pre-defined number of factors and exploratory factor analysis used for no pre-defined number of factors [147, 148]. Confirmatory factor analysis is to test whether the data fit a hypothesized measurement model, which is based on the previous analytic research [149] .

Exploratory factor analysis with the principal component analysis (PCA) method was used to identify dietary/nutrient patterns in this thesis. In the second research in this thesis (Chapter 5), PCA was applied to examine the association between dietary patterns and sleep outcomes. PCA aims to explain the total variation in intake of food groups in terms of a few linear functions called principals. Varimax rotation was used to improve the interpretability and minimize the correlation between the factors. Factor solutions that contain a different number of factors were tried. The final number of factors was determined by the eigenvalue greater than one, scree plot, and interpretability of the factors [150]. A higher score indicated greater association with the specific pattern. Similarly, PCA was also applied to generate nutrient patterns in the study included in Chapter 6 that examine the association with inflammation.

CHAPTER 4 ASSOCIATIONS BETWEEN MACRONUTRIENTS INTAKE AND SLEEP APNOEA AND SELF-REPORTED SLEEP SYMPTOMS

4.1 Publication

Cao, Y., Wittert, G., Taylor, A. W., Adams, R., & Shi, Z. (2016). Associations between Macronutrient Intake and Obstructive Sleep Apnoea as Well as Self-Reported Sleep Symptoms: Results from a Cohort of Community Dwelling Australian Men. *Nutrients*,*8*(4), 207.

Statement of Authorship

Title of Paper	Associations between macronutrients intake and obstructive sleep apnoea as well as self-reported sleep symptoms: results from a cohort of community dwelling Australian men
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Cao, Y., Wittert, G., Taylor, A. W., Adams, R., & Shi, Z. (2016). Associations between Macronutrient Intake and Obstructive Sleep Apnoea as Well as Self-Reported Sleep Symptoms: Results from a Cohort of Community Dwelling Australian Men. Nutrients, 8(4), 207.

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Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

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

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Article

Associations between Macronutrient Intake and Obstructive Sleep Apnoea as Well as Self-Reported Sleep Symptoms: Results from a Cohort of Community Dwelling Australian Men

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Received: 25 February 2016; Accepted: 30 March 2016; Published: 8 April 2016

Abstract: *Background:* macronutrient intake has been found to affect sleep parameters including obstructive sleep apnoea (OSA) in experimental studies, but there is uncertainty at the population level in adults. *Methods:* cross-sectional analysis was conducted of participants in the Men Androgen Inflammation Lifestyle Environment and Stress cohort (n = 784, age 35–80 years). Dietary intake was measured by a validated food frequency questionnaire. Self-reported poor sleep quality and daytime sleepiness were measured by questionnaires. Overnight in-home polysomnography (PSG) was conducted among participants with without previously diagnosed OSA. *Results:* after adjusting for demographic, lifestyle factors, and chronic diseases, the highest quartile of fat intake was positively associated with excessive daytime sleepiness (relative risk ratio (RRR) = 1.78, 95% CI 1.10, 2.89) and apnoea-hypopnoea index (AHI) ⩾20, (RRR = 2.98, 95% CI 1.20–7.38). Body mass index mediated the association between fat intake and AHI (30%), but not daytime sleepiness. There were no associations between other intake of macronutrient and sleep outcomes. *Conclusion:* high fat is associated with daytime sleepiness and AHI. Sleep outcomes are generally not assessed in studies investigating the effects of varying macronutrient diets on weight loss. The current result highlights the potential public health significance of doing so.

Keywords: macronutrient intake; fat intake; apnoea hypopnea index; polysomnography; daytime sleepiness

1. Introduction

A body of evidence has shown the associations between macronutrient intake and sleep parameters, however, with inconsistency. Carbohydrate, particularly with high glycaemic index (GI) was associated with faster sleep onset in healthy young men [1] but was associated with increased total arousal in children compared with low GI [2]. Low intake of protein (<16% *vs.* ⩾16%) has been shown to be associated with difficulty in initiating sleep, but high intake of protein (⩾19% *vs.* <19%) has been shown to be associated with difficulty maintaining sleep in middle-aged Japanese workers [3]. A fatty meal was found to aggravate apnoea in patients (overweight or obese) with obstructive sleep apnoea (OSA) [4]. A newly published randomized-crossover study by St-Onge's group found that low fibre and high saturated fat and sugar intake was associated with lighter sleep with more arousals in young and middle-aged healthy adults [5]. However, other studies suggested no association between

fat intake and sleep quality [6] or insomnia symptoms [3]. Although the inconsistent results may be attributed to a variety of study designs, uncertainty remains regarding the association between macronutrient intake and sleep in the current literature.

Studies that investigate the associations between macronutrient intakes and sleep parameters (objective measurements) at the population level in the community setting are desired. One study in Caucasian and Hispanic adolescents (n = 319) found that total fat intake was negatively associated in girls but positively associated in boys with rapid eye movement sleep [7]. However, there are no similar studies in adults. In this study, we aimed to assess whether macronutrient intake was associated with Apnoea-hypopnea Index (AHI) and self-reported sleep symptoms in community-dwelling middle-aged men at the population level under non-experimental conditions.

2. Methods

2.1. Study Population

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) cohort study was established in 2009, to investigate cardio metabolic disease risk factors in relation to sex steroids, inflammation, environmental and psychosocial factors in men. A detailed cohort profile has been published previously [8]. Briefly, the study population consists of 2563 community dwelling men aged 35–80 years at baseline (MAILES stage 1) from the harmonisation of two population cohort studies: all participants from the Florey Adelaide Male Ageing Study (FAMAS) (2002–2005) [9] and eligible male participants from the North West Adelaide Health Study (NWHAS) (2004–2006) [10]. The MAILES stage 2 (2007–2010) was an approximate five-year follow-up consisting of a Computer Assisted Telephone Interview (CATI), questionnaires and biomedical examinations. In total, 1815 men completed the dietary intake during stage 2.

MAILES stage 3, conducted in August 2010, consisted of a CATI including sleep related questions (n = 1629). The 184 who answered "yes" to the question "Have you ever been diagnosed with OSA with a sleep study" were excluded from participating in the sleep sub-study, and the 1445 men who answered "no" to the question were further asked if they were willing to participate in the sleep study (75.2% agreed). Of these, a random sample of 1087 was chosen for inclusion. A total of 857 had home based PSG (Figure 1 [11]), and 837 of them had final valid measurements and became the study population in this paper aimed at examining the association between macronutrient and AHI. Self-selection bias was examined by comparing those who underwent a sleep study with those men in the MAILES cohort who did not. Sleep study participants did not differ from non-participants in daytime sleepiness, waking frequency and obesity level but they were younger, and more likely to report frequent snoring and better general health [11]. Ethics approval was obtained from the Queens Elizabeth Hospital Human Ethics Committee for the NWHAS study (number 2010054) and the Royal Adelaide Hospital Human Research Ethics Committee for the FAMAS study (number 020305h).

2.2. Macronutrient Intake Assessment

Dietary intake was measured by the Cancer Council Victoria Diet Questionnaire for Epidemiological Studies (DQES-V3.1 (FFQ)). The FFQ has been validated in an Australian population and is widely used in epidemiological studies [12]. The questionnaire asks the participant's habitual consumption of 167 foods and six alcohol beverages over the previous 12-month on a 10-point frequency scale. Additional questions were asked about the type of breads, dairy products and fat spreads used. Macronutrient intakes were computed from the dietary data by the means of the nutrient composition tables in the NUTTAB95 database (Food Standards Australia New Zealand, Canberra, Australia, 1995).

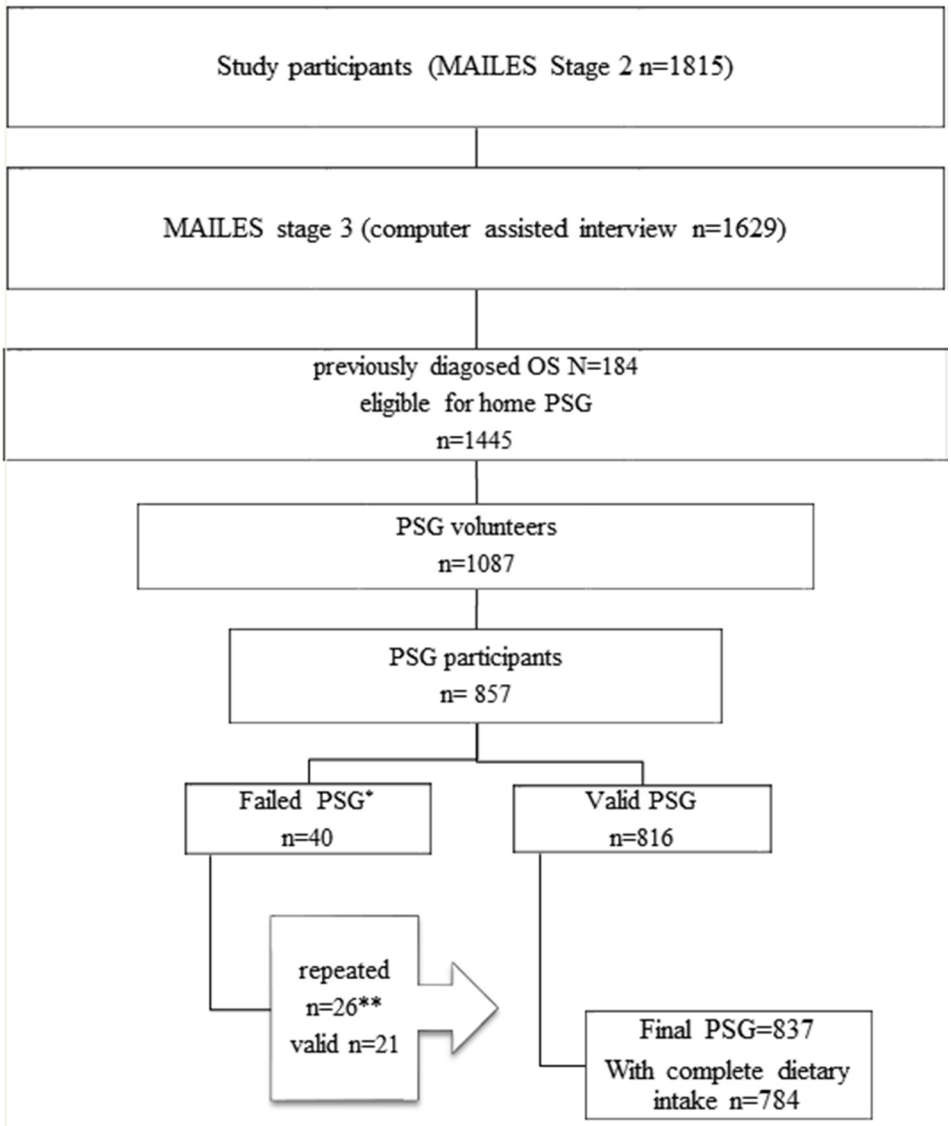

Figure 1. The flow chart of study participants with dietary intake (MAILES stage 2) and MAILES stage 3 with PSG recruitment * n = 21 total sleep time (TST) not ⩾3.5 h from ⩾5 h recording; n = 3 poor respiratory signals; n = 2 poor EEG; n = 14 no oxygen saturation (SaO_2); n = 3 all traces/recording failed. ** Includes 20 successful and 3 failed second PSG of which one was successfully reperated at a third time (this flow chart with instructions for PSG recruitment has been published previously [11]).

2.3. Sleep Assessments

Sleep measurements consisted of subjective (CATI and self-reported questionnaires) and objective (in-home PSG) approaches. Self-reported data included: (1) the STOP (snore, tiredness during daytime, observed apnoea and high blood pressure) questions [13]; (2) the Pittsburgh Sleep Quality Index (total score ranged from 0 to 21, a score >5 indicates poor sleep quality) [14]; and (3) sleepiness asked by the question "Do you feel sleepy when sitting quietly during the day or early evening? (1) yes (2) no (3) sometimes".

AHI was measured by a single overnight in-home PSG with Emblettas X100 portable sleep device [15]) and manually scored by an experienced sleep technician according to the 2007 American Academy of Sleep Medicine criteria (alternative) [16].

2.4. Other Measurements

Information on education, marital status, income, work status, physical activity, smoking, shift-work, and chronic diseases were collected by questionnaires [8]. Medication use was obtained from Medicare Australia by confidential unit record linkage, classified according to the Anatomical Therapeutic Chemical (ATC) Classification. The number of distinct medication classes (at the ATC third level) six months before clinical examination were treated as covariates.

Body weight was measured in light indoor clothing without shoes to the nearest 100 g. Height was measured without shoes to the nearest mm using a stadiometer. Waist circumference was measured to the nearest mm, midway between the inferior margin of the last rib and the crest of the ilium, in the mid-axillary line in a horizontal plane. Blood pressure was measured twice using a mercury sphygmomanometer on the right upper arm of the subject, who was seated for five minutes before the measurement.

2.5. Statistical Analysis

Macronutrient (carbohydrate, protein and fat) intakes (g) were recoded into quartiles (Q1–Q4). Chi square test was used to compare difference between categorical variables, and ANOVA was used to compare differences in continuous variables between groups. The association between quartiles of macronutrient intake and self-reported sleep (snoring and poor sleep quality) was assessed using Poisson regression. Multinomial logistic regression analysis was used to test the association between macronutrient intake and self-reported sleepiness ("yes", "sometimes" and "no"), as well as the association between macronutrient intake and AHI. AHI was divided into three categories: low (<5), medium (5–19) and high ($\geqslant$20). Using low level and the lowest quartile (Q1) of each macronutrient intake as the reference group, multivariate-adjusted associations were performed: (1) model 1 adjusted for age; (2) model 2 further adjustments for education, smoking, alcohol intake, physical activity and shift-work; (3) model 3 further adjustments for waist circumference, diabetes, depression and medication. We did a sensitivity analysis by further adjusting for energy intake in model 4. Structural equation modelling (SEM) was used to test whether body mass index (BMI) mediates the association between macronutrient intake and AHI (treated as continuous variable) and daytime sleepiness ("yes" was assigned with value 2, "no" was assigned with value 0, "sometimes" was assigned with value 1, and treated as continuous variables). Direct and indirect effects were estimated using command "estimate teffects". Linear trend across quartiles of each macronutrient intake was tested using the median value of each macronutrient intake (g) at each quartile and treating it as a continuous variable in the model. All statistical procedures were performed using STATA 13.0 (Stata Corporation, College Station, TX, USA).

3. Results

Overall, 1815 participants with dietary intake were analysed, of whom 837 without a prior diagnosis of OSA underwent successful sleep studies and 784 completed the dietary intake. Demographic characteristics by quartiles of each macronutrient intake of the participants are presented in Table 1. The mean age of the participants was 59.7 (SD 11.4) years. Characteristics of PSG participants with dietary intake are presented in Table S1.

Table 1. Characteristics of subjects according to quartiles of each macronutrient intake (n = 1815) [1].

Factors	Carbohydrate Intake (g)			Protein Intake (g)			Fat Intake (g)		*p*-Value
	Q1 (n = 454)	Q4 (n = 453)	*p*-Value	Q1 (n = 454)	Q4 (n = 453)	*p*-Value	Q1 (n = 454)	Q4 (n = 453)	
Age (years), mean (SD)	60.5 (11.7)	58.5 (11.4)	0.07	61.5 (12.1)	58.4 (10.9)	<0.001	59.9 (11.6)	59.5 (11.1)	0.47
Energy intake (kcal), mean (SD)	1539.1 (342.1)	2930.5 (606.7)	<0.001	1548.3 (348.4)	2900.5 (618.8)	<0.001	1535.1 (328.4)	2934.2 (596.9)	<0.001
Carbohydrates (g/day), mean (SD)	132.9 (26.0)	320.1 (91.5)	<0.001	157.5 (49.8)	283.1 (97.1)	<0.001	162.2 (51.2)	276.1 (93.0)	<0.001
Fat (g/day), mean (SD)	71.3 (22.2)	119.0 (34.7)	<0.001	66.5 (19.4)	123.4 (32.0)	<0.001	58.4 (10.9)	135.2 (25.8)	<0.001
Protein (g/day), mean (SD)	74.5 (23.1)	126.8 (37.1)	<0.001	64.1 (12.0)	141.6 (32.9)	<0.001	71.9 (19.0)	131.0 (39.0)	<0.001
Fibre (g/day), mean (SD)	18.4 (5.9)	37.7 (11.5)	<0.001	19.6 (7.3)	35.6 (11.0)	<0.001	21.2 (8.3)	34.3 (10.9)	<0.001
Body mass index (BMI), *n* (%)			0.71			0.003			0.49
<25	81 (18.7)	79 (18.2)		102 (23.4)	71 (16.3)		79 (18.2)	81 (18.6)	
25–30	214 (49.3)	207 (47.6)		211 (48.4)	201 (46.1)		214 (49.2)	192 (44.1)	
⩾30	139 (32.0)	149 (34.3)		123 (28.2)	164 (37.6)		142 (32.6)	162 (37.2)	
Income, *n* (%)			0.08			<0.001			0.16
Low income	171 (39.1)	153 (34.2)		193 (44.3)	153 (34.3)		163 (37.1)	164 (36.5)	
Middle income	113 (25.9)	156 (34.9)		113 (25.9)	165 (37.0)		120 (27.3)	164 (36.5)	
High income	130 (29.7)	114 (25.5)		105 (24.1)	104 (23.3)		134 (30.5)	102 (22.7)	
Not stated	23 (5.3)	24 (5.4)		25 (5.7)	24 (5.4)		22 (5.0)	19 (4.2)	
Marriage status, *n* (%)			0.003			0.014			0.07
Married or living with a partner	323 (74.1)	342 (77.0)		316 (72.6)	343 (77.1)		351 (80.1)	324 (72.5)	
Separated/divorced	70 (16.1)	50 (11.3)		65 (14.9)	53 (11.9)		46 (10.5)	74 (16.6)	
Widowed	19 (4.4)	11 (2.5)		24 (5.5)	13 (2.9)		16 (3.7)	18 (4.0)	
Never married	22 (5.0)	40 (9.0)		28 (6.4)	33 (7.4)		24 (5.5)	30 (6.7)	
Not stated/refused	2 (0.5)	1 (0.2)		2 (0.5)	3 (0.7)		1 (0.2)	1 (0.2)	
Education, *n* (%)			0.07			0.18			0.10
⩽High school	96 (25.3)	93 (23.3)		100 (27.0)	96 (24.2)		95 (25.1)	112 (28.1)	
Certificate	228 (60.2)	219 (54.9)		214 (57.8)	229 (57.8)		226 (59.6)	208 (52.1)	
Bachelor	52 (13.7)	83 (20.8)		50 (13.5)	69 (17.4)		53 (14.0)	75 (18.8)	
Not stated	3 (0.8)	4 (1.0)		6 (1.6)	2 (0.5)		5 (1.3)	4 (1.0)	
Current smoker, *n* (%)	71 (15.8)	51 (11.3)	0.22	62 (13.7)	66 (14.7)	0.35	48 (10.6)	61 (13.6)	0.36
Physical activity, *n* (%)			0.09			0.39			0.18
Sedentary	126 (30.6)	102 (24.2)		122 (29.4)	101 (24.0)		120 (28.7)	105 (24.9)	
Low exercise level	140 (34.0)	136 (32.2)		141 (34.0)	135 (32.1)		148 (35.4)	136 (32.3)	
Moderate exercise level	103 (25.0)	131 (31.0)		109 (26.3)	134 (31.8)		109 (26.1)	136 (32.3)	
High exercise level	43 (10.4)	53 (12.6)		43 (10.4)	51 (12.1)		41 (9.8)	44 (10.5)	
Depression, *n* (%)	37 (8.6)	56 (12.8)	0.17	33 (7.7)	61 (14.0)	0.016	38 (8.7)	64 (14.6)	0.029

[1] Macronutrient intake was divided into quartiles. Q1 and Q4 stand for the lowest and highest quartile. The results presented are unadjusted.

Univariate analysis results between macronutrient intake and AHI and self-reported sleep parameters are presented in Table 2. No association was found between carbohydrate or protein intake and AHI. High intake of fat was positively associated with high AHI and self-reported daytime sleepiness. The prevalence of sleepiness was 46.4% and 37.0% among those with highest and lowest quartiles of fat intake. The distribution of AHI was significantly different across quartiles of fat intake with high fat intake associated with high AHI.

The prevalence ratio of self-reported sleep parameters (relative risk ratio for sleepiness) across quartiles of macronutrient intake is presented in Table 3 and Figure S1. After adjusting for age, waist circumference, education, lifestyle factors (smoking, alcohol intake, physical activity and shift work), chronic diseases and medication, the highest quartile of fat intake was positively associated with daytime sleepiness. Compared with the lowest quartile, the highest quartile of fat intake had a relative risk ratio (RRR) of 1.78 (95% CI 1.10–2.89) for daytime sleepiness (p for trend across quartiles was 0.305). When further adjusted for total energy intake, the association was no longer significant. There were no associations between macronutrient intakes and other self-reported sleep parameters. The RRR for AHI using multinominal logistic regression are presented in Table 4 and Figure S2. After adjusting for age, waist circumference, lifestyle factors, chronic diseases and medication, fat intake was positively associated with high AHI ($\geqslant$20/h) (Q4 *vs.* Q1, RRR 2.98 (95% CI 1.20–7.38) (p for trend across quartiles was 0.046 across quartiles). Similarly, the association was not significant after further adjusting for total energy intake. BMI mediated 30% of the association between fat intake and AHI (direct effect 0.07, indirect effect 0.03, $p < 0.05$) (Table S2 and Figure S3). However, BMI did not mediate the association between fat intake and daytime sleepiness (Table S3).

Table 2. Polysomnography and self-reported sleep measures by quartiles of macronutrient intake in grams [1].

Sleep Parameters	Quartiles of Macronutrient Intake (g)				*p*-Value
	Carbohydrate Intake (g)				
Polysomnography measures (*n* = 784)	Q1 (*n* = 196)	Q2 (*n* = 196)	Q3 (*n* = 196)	Q4 (*n* = 196)	
Apnoea-Hypopnea Index (/h), *n* (%)					0.220
<5	48 (24.5)	40 (20.4)	49 (25.0)	32 (16.3)	
5–19	108 (55.1)	108 (55.1)	95 (48.5)	110 (56.1)	
⩾20	40 (20.4)	48 (24.5)	52 (26.5)	54 (27.6)	
Total sleep duration (min), mean (SD)	376.8 (57.5)	376.7 (54.6)	369.1 (59.2)	369.7 (62.3)	0.380
Self-reported measures	Q1 (*n* = 372)	Q2 (*n* = 372)	Q3 (*n* = 372)	Q4 (*n* = 372)	
Daytime sleepiness (*n* = 1487), *n* (%)	133 (35.7)	160 (43.1)	159 (43.0)	152 (40.8)	0.320
Poor sleep quality (*n* = 773)[2], *n* (%)	89 (48.4)	80 (42.6)	88 (46.1)	95 (50.5)	0.450
	Protein Intake (g)				
Polysomnography measures (*n* = 784)	Q1 (*n* = 196)	Q2 (*n* = 196)	Q3 (*n* = 196)	Q4 (*n* = 196)	
Apnoea-Hypopnea Index (/h), *n* (%)					0.230
<5	48 (24.5)	43 (21.9)	46 (23.5)	32 (16.3)	
5–19	104 (53.1)	109 (55.6)	105 (53.6)	103 (52.6)	
⩾20	44 (22.4)	44 (22.4)	45 (23.0)	61 (31.1)	
TST (min), mean (SD)	374.6 (55.8)	375.8 (57.3)	365.4 (55.8)	376.5 (64.2)	0.200
Self-reported measures	Q1 (*n* = 372)	Q2 (*n* = 372)	Q3 (*n* = 372)	Q4 (*n* = 372)	
Daytime sleepiness (*n* = 1487), *n* (%)	131 (36.1)	164 (43.6)	152 (39.9)	157 (42.8)	0.490
Poor sleep quality (*n* = 773), *n* (%)	95 (51.4)	76 (40.0)	93 (49.7)	88 (46.6)	0.130
	Fat Intake (g)				
Polysomnography measures (*n* = 784)	Q1 (*n* = 196)	Q2 (*n* = 196)	Q3 (*n* = 196)	Q4 (*n* = 196)	
Apnoea-Hypopnea Index (/h), *n* (%)					0.004
<5	45 (23.0)	45 (23.0)	51 (26.0)	28 (14.3)	
5–19	117 (59.7)	100 (51.0)	101 (51.5)	103 (52.6)	
⩾20	34 (17.3)	51 (26.0)	44 (22.4)	65 (33.2)	
TST (min), mean (SD)	374.4 (54.7)	373.2 (54.1)	375.8 (61.8)	368.8 (62.9)	0.660
Self-reported measures	Q1 (*n* = 372)	Q2 (*n* = 372)	Q3 (*n* = 372)	Q4 (*n* = 372)	
Daytime sleepiness (*n* = 1487), *n* (%)	137 (37.0)	151 (41.0)	144 (38.1)	172 (46.4)	0.051
Poor sleep quality (*n* = 773), *n* (%)	86 (45.5)	89 (46.8)	85 (46.4)	92 (48.7)	0.940

[1] Data are presented by macronutrient intake in quartiles of grams (unadjusted). Q1–Q4 = quartiles of each macronutrient intake in grams. Macronutrient intake for polysomnography measurements presented are from those with polysomnography measurements (*n* = 784). Macronutrient intake for self-reported sleep parameters are from those with self-reported day time sleepiness data (*n* = 1487); [2] poor sleep quality was measured among those who had polysomnography measurements (*n* = 784), macronutrient intake refers to polysomnography measured.

Table 3. The prevalence ratio (95% CI) for self-reported sleep parameters across quartiles of macronutrient intakes [1].

Self-reported Sleep Symptoms	Quartiles of Macronutrient Intake (g)				*n*
	Q1 (*n* = 372) ref	Q2 (*n* = 372)	Q3 (*n* = 372)	Q4 (*n* = 372)	
Daytime sleepiness [2]					
Carbohydrate					
Model 1	1.00	1.60 (1.08–2.37) *	1.69 (1.10–2.58) *	1.48 (0.89–2.46)	1487
Model 2	1.00	1.58 (1.02–2.46) *	1.40 (0.87–2.26)	1.33 (0.75–2.35)	1195
Model 3	1.00	1.46 (0.92–2.31)	1.25 (0.77–2.04)	1.19 (0.66–2.13)	1147
Model 4	1.00	1.31 (0.81–2.12)	1.05 (0.61–1.81)	0.85 (0.41–1.78)	1147
Protein					
Model 1	1.00	1.62 (1.09–2.40) *	1.29 (0.86–1.94)	1.59 (1.01–2.51) *	1487
Model 2	1.00	1.75 (1.13–2.74) *	1.32 (0.84–2.08)	1.74 (1.04–2.89) *	1195
Model 3	1.00	1.51 (0.96–2.40)	1.29 (0.81–2.06)	1.62 (0.96–2.74)	1147
Model 4	1.00	1.47 (0.91–2.36)	1.21 (0.71–2.05)	1.44 (0.73–2.86)	1147
Fat					
Model 1	1.00	1.53 (1.04–2.24) *	1.23 (0.83–1.80)	1.95 (1.28–2.99) **	1487
Model 2	1.00	1.59 (1.03–2.46) *	1.23 (0.80–1.87)	1.85 (1.15–2.96) *	1195
Model 3	1.00	1.53 (0.98–2.40)	1.12 (0.72–1.72)	1.78 (1.10–2.89) *	1147
Model 4	1.00	1.56 (0.97–2.53)	1.16 (0.69–1.95)	1.90 (0.93–3.91)	1147
Poor sleep quality					
Carbohydrate					
Model 1	1.00	0.89 (0.65–1.21)	0.97 (0.69–1.36)	1.08 (0.73–1.59)	751
Model 2	1.00	0.88 (0.61–1.27)	0.96 (0.66–1.40)	0.98 (0.62–1.54)	590
Model 3	1.00	0.90 (0.62–1.31)	0.94 (0.64–1.39)	0.95 (0.60–1.53)	569
Model 4	1.00	0.86 (0.58–1.28)	0.88 (0.57–1.36)	0.84 (0.47–1.51)	569
Protein					
Model 1	1.00	0.76 (0.56–1.04)	0.94 (0.69–1.28)	0.86 (0.60–1.23)	751
Model 2	1.00	0.77 (0.54–1.12)	0.92 (0.65–1.32)	0.89 (0.59–1.34)	590
Model 3	1.00	0.77 (0.53–1.13)	0.87 (0.60–1.26)	0.83 (0.55–1.27)	569
Model 4	1.00	0.74 (0.50–1.08)	0.79 (0.52–1.19)	0.69 (0.40–1.19)	569
Fat					
Model 1	1.00	1.03 (0.76–1.39)	1.02 (0.75–1.39)	1.07 (0.77–1.49)	751
Model 2	1.00	1.12 (0.79–1.60)	1.08 (0.76–1.55)	1.11 (0.75–1.63)	590
Model 3	1.00	1.06 (0.74–1.53)	0.98 (0.68–1.42)	1.01 (0.68–1.51)	569
Model 4	1.00	1.01 (0.69–1.48)	0.90 (0.59–1.38)	0.86 (0.49–1.51)	569

[1] Poisson regression was performed for self-reported poor sleep quality and incidence rate ratio is presented; [2] multinomial logistic regression was performed for daytime sleepiness as it has three levels: "yes", "sometimes", and "no", and the results were showing those who answered "yes" compared with "no". Four models adjusted for different covariates are presented. Model 1: adjusted for age. Model 2: further adjusted for education (high school, certificate and bachelor), smoking (yes/no), alcohol intake (standard drinks 0, 1, 3), physical activity (sedentary, low, moderate and high), shift work (yes/no). Model 3: further adjusted for waist circumference (continuous), depression (yes/no), diabetes (yes/no), and medication (continuous). Model 4: further adjusted for energy intake. * $p < 0.05$, ** $p < 0.01$.

Table 4. The associations between macronutrient intake and Apnoea hypopnea index (AHI) [1].

AHI Categories	Models	Quartiles of Macronutrient Intake (g)				*n*
		Q1 (ref)	Q2	Q3	Q4	
AHI (/h)				***Carbohydrate***		
<5 (ref)	Model 1	1.00	1.00	1.00	1.00	169
5–19	Model 1	1.00	1.22 (0.72–2.06)	0.80 (0.45–1.41)	1.36 (0.67–2.74)	421
⩾20	Model 1	1.00	1.36 (0.72–2.54)	0.96 (0.49–1.89)	1.27 (0.55–2.89)	194
						Subtotal: 784
<5 (ref)	Model 2	1.00	1.00	1.00	1.00	127
5–19	Model 2	1.00	1.79 (0.96–3.33)	1.21 (0.63–2.33)	1.77 (0.78–3.99)	338
⩾20	Model 2	1.00	1.60 (0.76–3.38)	1.17 (0.54–2.54)	1.55 (0.60–4.02)	155
						Subtotal: 620
<5 (ref)	Model 3	1.00	1.00	1.00	1.00	123
5–19	Model 3	1.00	1.82 (0.94–3.52)	1.12 (0.57–2.21)	1.70 (0.73–3.95)	324
⩾20	Model 3	1.00	1.44 (0.64–3.25)	1.07 (0.46–2.46)	1.47 (0.53–4.11)	149
						Subtotal: 596
<5 (ref)	Model 4	1.00	1.00	1.00	1.00	123
5–19	Model 4	1.00	1.59 (0.79–3.20)	0.87 (0.39–1.93)	1.15 (0.40–3.34)	324
⩾20	Model 4	1.00	1.06 (0.45–2.49)	0.62 (0.24–1.60)	0.56 (0.16–2.05)	149
						Subtotal: 596
				Protein		
<5 (ref)	Model 1	1.00	1.00	1.00	1.00	169
5–19	Model 1	1.00	1.20 (0.72–2.01)	1.09 (0.64–1.85)	1.51 (0.79–2.87)	421
⩾20	Model 1	1.00	1.09 (0.59–2.03)	1.04 (0.55–1.97)	1.80 (0.86–3.78)	194
						Subtotal: 784
<5 (ref)	Model 2	1.00	1.00	1.00	1.00	127
5–19	Model 2	1.00	1.44 (0.78–2.67)	1.18 (0.63–2.20)	1.96 (0.92–4.18)	338
⩾20	Model 3	1.00	1.21 (0.57–2.54)	1.00 (0.48–2.12)	2.40 (1.00–5.76) *	155
						Subtotal: 620
<5 (ref)	Model 3	1.00	1.00	1.00	1.00	123
5–19	Model 3	1.00	1.22 (0.64–2.32)	0.99 (0.51–1.89)	1.63 (0.74–3.56)	324
⩾20	Model 3	1.00	1.03 (0.46–2.32)	0.83 (0.36–1.87)	2.03 (0.79–5.22)	149
						Subtotal: 596
<5 (ref)	Model 4	1.00	1.00	1.00	1.00	123
5–19	Model 4	1.00	1.09 (0.55–2.14)	0.79 (0.37–1.69)	1.13 (0.41–3.10)	324
⩾20	Model 4	1.00	0.83 (0.36–1.93)	0.54 (0.21–1.38)	0.99 (0.29–3.32)	149
						Subtotal: 596

Table 4. *Cont.*

				Fat		
<5 (ref)	Model 1	1.00	1.00	1.00	1.00	169
5–19	Model 1	1.00	0.85 (0.51–1.40)	0.74 (0.45–1.23)	1.25 (0.68–2.30)	421
⩾20	Model 1	1.00	1.49 (0.80–2.77)	1.09 (0.58–2.06)	2.46 (1.21–5.00) *	194
						Subtotal: 784
<5 (ref)	Model 2	1.00	1.00	1.00	1.00	127
5–19	Model 2	1.00	0.84 (0.46–1.55)	0.67 (0.37–1.21)	1.33 (0.65–2.73)	338
⩾20	Model 3	1.00	1.61 (0.77–3.40)	1.10 (0.52–2.30)	2.67 (1.15–6.20) *	155
						Subtotal: 620
<5 (ref)	Model 3	1.00	1.00	1.00	1.00	123
5–19	Model 3	1.00	0.83 (0.44–1.55)	0.66 (0.36–1.22)	1.40 (0.66–2.96)	324
⩾20	Model 3	1.00	1.54 (0.69–3.46)	1.20 (0.54–2.67)	2.98 (1.20–7.38) *	149
						Subtotal: 596
<5 (ref)	Model 4	1.00	1.00	1.00	1.00	127
5–19	Model 4	1.00	0.67 (0.34–1.33)	0.46 (0.21–1.00) *	0.76 (0.26–2.23)	334
⩾20	Model 4	1.00	1.25 (0.53–2.97)	0.84 (0.32–2.21)	1.63 (0.45–5.90)	154
						Subtotal:596

[1] The results were from multinomial logistic regression. It presents comparing with the lowest level of sleep outcome, the relative risk ratio for medium or high level of having higher quartile of each macronutrient intake comparing with the lowest quartile of intake (Q2–4 *vs.* Q1). Four models adjusted for different covariates are presented. Model 1: adjust for age. Model 2: further adjusted for education (high school, certificate and bachelor), smoking (yes/no), alcohol intake (standard drinks 0, 1, 3), physical activity (sedentary, low, moderate and high), shift work (yes/no). Model 3: further adjusted for waist circumference (continuous), depression (yes/no), diabetes (yes/no), and medication (continuous). Model 4: further adjusted for energy intake. * $p < 0.05$.

4. Discussion

To the best of our knowledge, this is the first study to assess the association between macronutrient intake and sleep in a large population based cross-sectional study using objectively measured polysomnography. We found that high intake of fat was associated with daytime sleepiness and high AHI. The associations between fat intake and AHI was mediated by BMI.

Although the mechanism of the associations between macronutrient intake and sleep parameters is yet to be clear, some possibilities have been suggested by previously published work. Sleep can be regulated by various hormones that is induced by food intake through communications between hypothalamus and the brain [17]. Both dietary carbohydrates and protein can affect tryptophan metabolism through the availability tryptophan uptake into the brain via the blood brain barrier [18]. Regarding the mechanism of fat intake and sleep parameters, it is suggested that fat may affect sleep by altering circadian regulation of hormonal, central nervous and metabolic systems [19].

We found a positive association between high fat intake and daytime sleepiness. Early experimental studies showed that both infusion of lipid into the small intestine and isoenergetic meals may cause a decline in alertness and concentration [20]. Wells et.al have shown that healthy young subjects felt sleepier and less awake 2–3 h after a high-fat-low-carbohydrate meal [21]. Although carbohydrate rich meals have been demonstrated to be associated with postprandial lassitude [22], a greater decline was seen in high fat intake [20]. Other laboratory evidences suggested the potential role of gut neuro hormones in promoting hypnogenesis through vagal activation which essentially triggers fatigue [23–27]. However, we did not have data on the timing of fat intake, and dietary data collection was prior to sleep measurements, so the immediate effect of sleepiness of high-fat diet was not able to be assessed. Long-term high fat intake may lead to elevated levels of leptin and decreased levels of ghrelin [28], which could regulate arousal and wakefulness via orexin [29]. Increased sleepiness was observed in mice with high-diet fed induced obesity [30]. In large scale studies, positive associations between obesity and excessive daytime sleepiness has been reported [31,32]. This is consistent with our data that participants in the obese group had a higher risk of daytime sleepiness after adjusting for lifestyle factors (Table S4). However, obesity does not seem to be a mediator of the association between fat intake and daytime sleepiness (Table S3).High fat intake was also found to be associated with a high level of AHI ($\geqslant$20/h) in this study, after adjusting for age, waist, lifestyle factors, chronic diseases and medication. Similarly, previous experimental studies found a fatty meal the night before bed would increase AHI in OSA patients [4]. Long-term effect of high-fat diet on AHI is not clear. In non-obese rats, high-fat fed diet increases apnoea, and this could be reversed and prevented by a low dose injection of metformin (a drug for insulin resistance) [33]. This may suggest that insulin resistance induced by high fat diet may be one of the mechanisms leading to increased AHI, but was dependent on body weight. In patients with type 2 diabetes, AHI ($\geqslant$30/h) was associated with higher BMI [34]. Obesity has been suggested as one of the main risk factors of sleep apnoea [35] in the literature. In our study, being obese was strongly associated with higher AHI compared with non-obese participants (Table S5). Our mediation modelling suggests that the direct effect of BMI on AHI was about five times stronger than the effect from fat intake, and about 30% of the effect on AHI comes from BMI (Table S2 and Figure S3).

Regarding energy intake, higher energy intake was associated with high level of AHI in our study (Table S5), and our sensitivity analysis suggested that it was a confounder in the association between fat intake and AHI and daytime sleepiness. However, energy intake estimated from self-reported dietary intake has been suggested to be less accurate [36]. Moreover, soft drink and alcohol were not included in the energy intake calculation in our study.

The main merits of this study are: (1) it is the first investigation of the association between macronutrient intake and PSG measured sleep parameters as well as self-reported sleep problems in a relatively large sample; (2) we were able to adjust for a wide range of covariates including age, waist circumference, energy intake, education, smoking, alcohol intake, physical activity, shift work, depression, diabetes and medication.

Several limitations in our study need to be acknowledged. Firstly, asynchronous exploration between macronutrient and sleep were performed due to the mismatch of time of the PSG study and dietary survey. Secondly, due to the nature of the cross-sectional study, causation cannot be made. Thirdly, because the study only involved men, the findings may not be generalised to women. In addition, we only conducted one overnight PSG assessment as it is not practical to have multiple night PSG assessments in large epidemiological studies. Despite objective sleep measurement, dietary intake was estimated by FFQ, rather than 24-h food recall or actual weighing. 24-h food recall provides meal specific food intake information, which has been suggested to be associated with circadian adaption [37]. However, it is impractical to conduct 24-h food recall in studies with large sample size, and 24-h recall does not capture a long term dietary habit as FFQ does.

In conclusion, high fat intake was associated with daytime sleepiness and high AHI. BMI mediates the association between fat and AHI but not daytime sleepiness. Although a public health benefit is suggested, future studies are needed to confirm the findings at the population level.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/8/4/207s1.

Acknowledgments: The present study was supported by the National Health and Medical Research Council of Australia (NHMRC Project Grant 627227).

Author Contributions: Y.C., A.W.T., G.W., R.A. and Z.S. conceived and designed the study; Y.C. analyzed the data; G.W., A.W.T., R.A. and Z.S. contributed materials/analysis tools; Y.C. wrote the paper.

Conflicts of Interest: The authors declared that there are no conflicts of interest.

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CHAPTER 5 DIETARY PATTERN AND SLEEP PARAMETERS

5.1 Publication

Cao, Y., Taylor, A. W., Wittert, G., Adams, R., & Shi, Z. (2016). Dietary pattern and sleep parameters in a cohort of community dwelling Australian men. Asia Pacific Journal of Clinical Nutrition (Accepted)

Statement of Authorship

Title of Paper	Dietary pattern and sleep parameters in a cohort of community dwelling Australian men.
Publication Status	☐ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Cao, Y., Taylor, A. W., Wittert, G., Adams, R., & Shi, Z. (2016). Dietary pattern and sleep parameters in a cohort of community dwelling Australian men. Asia Pacific Journal of Clinical Nutrition (Accepted)

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Contribution to the Paper	Conception and design, statistical analysis, interpretation of data, manuscript preparation, and critical revision of the manuscript.
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 26/10/2016

Co-Author Contributions

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

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

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

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

Name of Co-Author	Gary Wittert
Contribution to the Paper	Conception and design, interpretation of results, critical manuscript evaluation and editing. Contribution to the materials/analysis tools.
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5.2 Abstract

Background: Emerging evidence suggests potential effects of nutrients/foods on sleep parameters. However, no studies have addressed the complex interactions among nutrients/foods and relate them to sleep outcomes.

Objective: To investigate the associations between dietary patterns and sleep parameters (polysomnography (PSG) measured and self-reported sleep symptoms) in a large sample of community dwelling men in South Australia.

Methods: Cross-sectional analysis was conducted of participants in the Men Androgen Inflammation Lifestyle Environment and Stress cohort enrolled in a sleep sub-study (n=784, age 35-80 years). Dietary intake was measured by a validated food frequency questionnaire. Dietary patterns were identified by factor analysis. Sleep was assessed by an overnight home PSG and self-reported questionnaires.

Results: Two factors were obtained by factor analysis: Factor 1 is characterized by high intakes of vegetables, fruits, and legumes and factor 2 is characterized by processed meat, snacks, red meat and take-away foods. Three categories of the dietary patterns were defined (prudent, mixed and western) through classification of the sample according to the actual consumption higher or lower of each factor**.** The prudent (factor 1 dominant) and mixed dietary patterns were inversely associated with sleep onset, compared with the western dietary pattern (factor 2 dominant) (β=-6.34 (95% CI-1.11, -11.57), β=-4.34 (95%CI-8.34, -0.34) respectively). The association was only significant with the prudent dietary pattern after multiple comparison adjustment. No associations were found with between dietary patterns and other sleep outcomes.

Conclusions: The prudent dietary pattern is associated with a faster sleep onset, which may provide a solution for sleep management.

Keywords: dietary patterns, polysomnography, sleep onset latency, apnoea hypopnea index, men

5.3 Introduction

In line with the epidemic of sleep disturbances [151], Australians have demonstrated a high prevalence of frequent sleep difficulties (including sleep initiating and maintenance, and inadequate sleep), daytime fatigue and daytime sleepiness (20-35%) [152]. Sleep disturbances are well known to increase the risk of obesity, type 2 diabetes and inflammation [153].

Short sleep has been shown to be associated with higher intakes of energy-rich foods mostly from fat or refined carbohydrates [22, 77, 103]. On the other hand, as the bidirectional relationship between food intake and sleep, diet may also affect sleep although findings are inconsistent [24]. Experimental studies have found that carbohydrate intake, particularly with high glycaemic index (GI) before bedtime, was associated with shortened sleep onset in healthy young men [25], but was associated with increased arousals in toddlers [70]. In observational studies, low intake of protein (<16% of energy intake vs ≥ 16% of energy intake) was associated with poor sleep quality, while high protein intake (≥19% of total energy vs <19% of energy intake) was associated with difficulties of maintaining sleep.[29] Another two studies did not find any association between protein intake and sleep duration/quality [72, 74].

Most of the existing studies on diet and sleep mainly focused on specific nutrients/foods intake. However, foods are consumed in combination and neglecting the interactions among nutrients/foods may generate inconsistent results. Dietary pattern analysis can address the possible interactions among foods and nutrients, connecting diet with health outcomes [32].

Dietary patterns have been shown to be associated with metabolic syndrome [33], depression [34], stroke [35] and mortality [36] in adults. However, the association between

dietary patterns and sleep is not well studied. Currently, only two studies have assessed the association between dietary patterns and subjective measured sleep. Dietary pattern rich in fruits and vegetables was positively associated with long sleep duration among Portuguese children [87]. A healthy dietary pattern was inversely associated with difficulty initiating sleep among Japanese adults [88]. No studies on dietary patterns and objectively measured sleep are available.

We aimed to investigate the association between dietary patterns and polysomnography (PSG) measured sleep onset latency (SOL), sleep duration and Apnoea-Hypopnea Index (AHI) and as well as self-reported sleep symptoms in a large sample of community men in South Australia.

5.4 Methods

5.4.1 Study population

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study is an ongoing cohort study established in 2009 investigating the roles of sex steroids, inflammation, environmental and psychosocial factors in the pathogenesis of cardio-metabolic disease in men. A detailed cohort profile has been published previously [154]. Briefly, MAILES contains 2563 men aged 35-80 years old from Adelaide at baseline (MAILES stage 1) from the harmonisation of two population cohort studies: all participants from the Florey Adelaide Male Ageing Study (FAMAS) (2002-05) [130] and eligible male participants from the North West Adelaide Health Study (NWHAS) (2004-06) [131]. The MAILES stage 2 was an approximate five-year follow-up consisting of questionnaires and biomedical examinations. In total, 1815 men provided details on dietary intake during MAILES stage 2.

MAILES stage 3, consisting of a Computer Assisted Telephone Interview (CATI) that included sleep related questions, was conducted in August 2010 (n=1629). The 184 who answered 'yes' to the question 'Have you ever been diagnosed with obstructive sleep apnoea (OSA) with a sleep study' were excluded from participating in the sleep study, and 1445 men who answered 'no' to the question were further asked if they were willing to participant the sleep study (75.2% agreed). Of these, a random sample of 1087 was chosen for inclusion. A total of 857 men underwent PSG (Figure 5.1 [155]) by the end of the study period. Ethics approval was obtained from the Queens Elizabeth Hospital Human Ethics Committee for the NWHAS study (number 2010054) and the Royal Adelaide Hospital Human Research Ethics Committee for the FAMAS study (number 020305h).

5.4.2 Dietary measurements

Dietary intake was measured by the Cancer Council of Victoria Diet Questionnaire for Epidemiological Studies (DQES-V 3.0 & 3.1 (FFQ)). The FFQ has been validated in an Australian population and is widely used in epidemiological studies [135]. The questionnaire asks the participant's habitual consumption of 167 food items and six alcohol beverages over the last 12-month on a 10-point frequency scale. By using the estimated portion sizes and frequencies, the intake of each food (in grams) was converted to daily equivalents for analyses. Additional questions were asked about the type of breads, dairy products and fat spreads.

5.4.3 Sleep measurements

Sleep measurements consisted of subjective (CATI and self-completed questionnaires) and objective (in-home PSG) approaches. Self-reported data includes: 1) the STOP questionnaire - questions of snoring, tiredness during daytime, observed apnoea and high blood pressure [136]; 2) the Pittsburgh Sleep Quality Index (PSQI) - total score of PSQI

ranged from 0-21, with a score >=5 interpreted as poor sleep quality [54]; 3) and sleepiness asked by the question 'Do you feel sleepy when sitting quietly during the day?'

Among those without previous diagnosis of OSA, an overnight in-home PSG with Emblettas X100 portable sleep device (http://www.embla.com/index.cfm/id/57/Embletta-X100/) was conducted with manual scoring undertaken by an experienced sleep technician according to the current American Academy of Sleep Medicine criteria (alternative) [156]. Several detections were monitored by PSG including electroencephalography, electrooculography, electromyography, and electrocardiograms, thoracic and abdominal bands for respiratory effort, a nasal pressure cannula for nasal airflow, a body-position sensor for body posture, and a finger oximeter sensor to monitor oxygen saturation. PSG parameters used in the analysis were SOL, total sleep duration and AHI.

5.4.4 Other measurements

Information on education, marital status, income, work status, physical activity, smoking, shift-work and chronic diseases were collected by questionnaires [154]. Medication use was obtained from Medicare Australia by confidential unit record linkage, classified according to the Anatomical Therapeutic Chemical (ATC) Classification. The number of distinct medication classes (at the ATC third level) six months before the clinical examination were treated as covariates.

Body weight was measured in light indoor clothing without shoes to the nearest 100 grams. Height was measured without shoes to the nearest mm using a stadiometer. Waist circumference was measured to the nearest mm midway between the inferior margin of the last rib and the crest of the ilium, in the mid-axillary line in a horizontal plane. Blood pressure was measured twice by mercury sphygmomanometer on the right upper arm of the subject, who was seated for five minutes before the measurement.

5.4.5 Statistical analyses

The 167 food items were grouped into 41 groups, with modifications made based on a study that followed the Australian dietary guideline [157]. Dietary patterns were identified using factor analysis (principle-component method) with estimated daily intake (by grams) of the 41 food groups. Varimax rotation was used to improve interpretability and minimize the correlation between the factors. Factor solutions that contain a different number of factors were also tried. The final number of factors was determined by eigenvalue >1, scree plot, and interpretability of the factors [150]. Factor loadings for each food group were calculated and factor scores for each pattern were calculated for each participant by summing the total intake of the 41 food groups (standardised) weighted by their factor loadings. A higher score indicated greater association with the specific pattern.

Factor scores were used to categorize the sample and to carry out the statistical analysis. Chi square test was used to compare difference between categorical variables, and ANOVA was used to compare differences in continuous variables between groups. Poisson regressions were used to examine the association between dietary patterns and self-reported sleep symptoms. Linear regression models were used to examine the associations between dietary patterns and sleep parameters (SOL, AHI and PSG measured sleep duration). Tukey's honestly significant difference (HSD) was performed to adjust for multiple comparisons. A set of models were conducted: 1) adjusted for age; 2) further adjusted for education, smoking, alcohol consumption, physical activity and shift-work; 3) further adjusted for waist circumference; 4) further adjusted for diabetes, depression and medication. Sensitivity analyses were conducted using the same models between separate factors from factor analysis and sleep parameters. All of the analyses were performed using

STATA 13.0 (Stata Corporation, College Station, TX, USA) with a p value of <0.05 as statistical significance.

5.5 Results

At the completion of MAILES stage 2 there were 1815 participants with a complete set of data including dietary intake, of whom 82% had self-reported daytime sleepiness data. In the sleep sub study, 784 had home PSG data that was technically satisfactory, and 99% had self-reported poor sleep quality data (asked among PSG participants).

The factor analysis identified two main factors, and loadings of each factor were shown in Figure 5.2. Factor 1 was characterized by high intake of vegetables, fruits, and legumes while factor 2 was characterized by high intake of processed meat, snacks, red meat and take away foods. The food groups according to the two factors are presented in Supplemental Table 5.1, and the food groups according to three dietary patterns that based on the differences of the quartiles of factors between the two factors are presented in Supplemental Table 5.2. Sensitivity analysis of the association between two factors separately with PSG sleep parameters is presented in Supplemental table 5.3.

Although the two factors are independent statistically, in reality, people with high intake of one factor may have low intake of the other. Therefore, the sample was categorised according to the difference of the quartiles of the factor scores between the two factors. If the difference of the quartiles >=2, these subjects were grouped into either factor 1 dominant (named as the ‘prudent pattern’) or factor 2 dominant pattern (named as the ‘western pattern’). The rest of the subjects were grouped as the ‘mixed pattern’. The number of subjects in each group were as following: the prudent pattern, n=312 for the whole sample, and n=130 for subjects with PSG; the western dietary pattern, n=347 for the whole sample,

and n=145 for subjects with PSG; the mixed dietary pattern, n=1156 for the whole sample, and n=509 for subjects with PSG.

The age adjusted sample characteristics by dietary patterns in the three categories are presented in Table 5.1. Subjects with the prudent dietary tended to be older, lighter, less depressed, higher educated, and have lower consumption of alcohol, cigarettes, macronutrient and total energy intake and were more active.

Age adjusted sleep parameters by dietary patterns are presented in Table 5.2. Subjects with the prudent dietary had the shortest SOL comparing with those who had mixed or the western patterns (16.3 min vs 19.2 min and 22.5 min) (p=0.024). Although without statistical significance, subjects with the prudent dietary pattern had the lowest AHI comparing with those who had mixed or the western patterns (14.4 vs 14.8 and 17.0). Total sleep duration did not differ by the three dietary patterns. For self-reported sleep measures, no differences were found in daytime sleepiness and poor sleep quality according to dietary patterns. No associations were found between dietary patterns and self-reported sleep symptoms (Table 5.3).

After adjusting for age, demographic and lifestyle factors, weight, as well as chronic diseases, the prudent dietary pattern was associated with about six minutes less in SOL compared with the western dietary pattern (β=-6.34, 95% CI-1.11, -11.57). Similarly, the mixed pattern was also associated with about four minutes less in SOL compared with the western dietary pattern (β=-4.34, 95% CI-8.34, -0.34). No associations were observed between the prudent dietary pattern or the western dietary pattern and other PSG outcomes (Table 5.4).

Multiple comparisons adjustment suggested that the prudent dietary pattern was still inversely associated with SOL ($p<0.05$) (data not shown), while the association between the mixed dietary pattern and SOL was not significant after adjustment.

5.6 Discussion

To the best of our knowledge, this is the first study assessing the association between dietary patterns and objectively measured sleep parameters in a relatively large community cohort. The prudent and the mixed dietary pattern were associated with a reduced SOL. No associations were observed between the dietary patterns and any other sleep outcomes.

We have divided the sample according to the real consumption of two factors obtained by factor analysis. Similarly, San-Cristobal *et. al.* [158] have previously categorized the sample into four groups (prudent, healthy, western and compensatory) based on the adherence to the two factors that derived from factory analysis. We compared the results with using the original two factors as two patterns separately in the analysis and the results remained (Supplemental Table 5.3).

Previous studies have suggested that dietary factors could affect sleep architecture such as shortening sleep latency and increasing non rapid eye movement sleep [159-161]. Afaghi's group has reported that a meal with high glycaemic index resulted in a reduced SOL compared with low glycaemic meal in 12 healthy young men [25]. They indicated the main mechanism was to do with the increased insulin response and the ratio of tryptophan to large neutral amino acid. This experimental result is in line with our study showing that the prudent dietary pattern was associated with a shortened SOL. As root vegetables are highly loaded on the prudent dietary pattern, the reduced SOL may also be explained by high glycaemic index. However, as dietary patterns do not reveal the timing of food intake, the

direct effect of the prudent dietary pattern on SOL is unclear. In a Japanese study of adult workers, healthy dietary pattern was inversely associated with difficulty in initiating sleep [88]. Although they did not measure SOL, the inverse association between a healthy dietary pattern and difficulty in sleep initiation was in line with our findings. Although the biological mechanisms linking dietary patterns and SOL are yet to be explored, depression may be one of the possible mediators. A systematic review has found that a healthy dietary pattern was associated with reduced odds of depression [162] possibly due to its anti-inflammatory properties [163-165]. It is known that sleep quality is influenced by psychological factors such as anxiety [166] and depression [167] We speculate that the antidepressant/anti-inflammatory effect of the prudent dietary pattern may partly explain the reduced SOL. It is noted that when we tested the association between two separate factors and SOL, factor 1 was inversely associated with SOL across quartiles (Supplemental Table 3). This is consistent with categorizing into three patterns (prudent, mixed and western) in the current analysis, which highlighted the dominant patterns consumed in the sample.

Trakada *et. al.* [27] assessed the role of a fatty meal on OSA in 19 subjects and reported that a fatty meal was associated with increased AHI. However, the small sample size and non-randomised control study design were the main limitations to that study. In our study, there was a positive association between factor 2 (high intake of processed meat, snacks, red meat and take away foods) and AHI after adjusting for demographic and lifestyle factors (Supplemental Table 5. 3). This is consistent with our previous finding that a high intake of fat was associated with an increased number of AHI [168].

Self-reported total sleep duration has been suggested to be inversely associated with high fat/ energy intake [22, 169] and high fat intake has been shown to be associated with short sleep although the association was weaker [22]. However, dietary patterns were not

associated with PSG measured total sleep duration in our data. A possible reason could be the differences between actual measured and self-reported sleep duration.

No association was found between daytime sleepiness and the dietary patterns. Postprandial sleepiness has been suggested in early experimental studies, [170] which could be explained by the interactions with the gut neuro hormones and promoting hypnogenesis [171]. A healthy dietary pattern that is characterized by vegetables, mushrooms, potatoes, seaweeds, soy products and eggs was associated with a decreased risk of difficulty of initiating sleep among Japanese workers [88], However it is unknown how such dietary patterns would be associated with daytime sleepiness as it was not assessed in that study. Moreover, despite the existence of common elements, dietary patterns vary among populations, and the differences in relation to sleep parameters should be taken into account.

The strengths of this study are the used of valid dietary questionnaire, large size of the cohort, detailed information related to potential confounding factors and the objective measurements of sleep. There are a number of limitations in this study. Firstly, as the study is cross-sectional, casual effect cannot be indicated. Secondly, although we derived two factors from the factor analysis, we arbitrarily divided them into three groups according to the distribution of the sample. However, the result is consistent with using two factors separately. Finally, we only conducted one overnight PSG assessment as it is not practical to have multiple night PSG assessments in large epidemiological studies. Because the data was limited to males, we do not know what the associations are in females.

In conclusion, a prudent dietary pattern with high intake of vegetables, fruits, and legumes was associated reduce SOL. Although this may assist in promoting diet interventions to improve sleep for clinicians, further prospective studies are needed to confirm these findings.

5.7 Acknowledgments

The present study was supported by the Australian National Health and Medical Research Council (NHMRC Project Grant 627227) and Meat & Livestock Australia. The authors' contributions are as following: Y.C carried out the data analyses and wrote the manuscript; Z.S and G.W contributed to conceiving the study design, reviewing the data analyses; G.W, Z.S and AWT critically reviewed the manuscript and approved the final version.

The authors declared that there are no conflicts of interest

Table 5. 1 Age-adjusted sample characteristics by dietary patterns [1]

	Western pattern (n=347)	Mixed pattern (n=1156)	Prudent pattern (n=312)	p-value [2]
Age (years)	55.8 (0.6)	59.7 (0.3)	63.6 (0.6)	<0.001
BMI (kg/m^2)	29.3 (0.3)	28.8 (0.1)	28.4 (0.3)	0.06
Waist circumference (cm)	103 (0.7)	101 (0.4)	99.1 (0.7)	<0.001
Carbohydrate (g/d)	235 (4.5)	212 (2.5)	217 (4.8)	<0.001
Protein (g/d)	110 (1.8)	98.8 (1.0)	93.0 (1.9)	<0.001
Fat (g/d)	110 (1.6)	92.8 (0.9)	79.1 (1.7)	<0.001
Energy intake (kcal)	2464 (34.4)	2157 (18.7)	2012 (36.3)	<0.001
Alcohol (standard drinks)	2.5 (0.2)	1.6 (0.1)	1.1 (0.2)	<0.001
Smokers (%)	25.0	11.4	5.9	<0.001
Depression (%)	14.2	11.3	6.8	0.01
Diabetes (%)	13.0	14.4	14.5	0.82
Physical active [3] (%)	67.2	78.6	87.9	<0.001
Higher education [4] (%)	70.0	74.6	82.2	0.003
Shift worker (%)	48.9	49.6	49.2	0.97

[1] Results are presented in mean (SE) for such values.
[2] p values were from ANOVA analysis adjusting for age.
[3] Physical active was defined as those who reported not being sedentary.
[4] Higher education was defined as those who reported have obtained trade or bachelor degree or higher.
BMI, body mass index.

Table 5. 2 Age-adjusted sleep outcomes by dietary patterns [1]

	Western pattern	Mixed pattern	Prudent pattern	p-value [2]
PSG measured	n=145	n=509	n=130	
AHI (/h)	17.0 (1.2)	14.8 (0.6)	14.4 (1.2)	0.19
Sleep onset latency (min)	22.5 (1.6)	19.2 (0.8)	16.3 (1.7)	0.024
Total sleep duration (min)	372 (4.8)	373 (2.6)	374 (5.1)	0.96
Self-reported	n=252	n=940	n=295	
Daytime sleepiness (%)	43.6	41.6	33.6	0.07
Poor sleep quality [3] (%)	52.0	47.9	37.5	0.06

[1] Results are presented in mean (SE) for such values.
[2] p values were from ANOVA analysis adjusting for age.
[3] Poor sleep quality was measured in MAILES participants who participated PSG, the number of participants in each pattern refers to the numbers for PSG measured in the table.
AHI, apnea-hypopnea index

Table 5. 3 Prevalence ratio of self-reported sleep outcomes by dietary patterns [1]

	Western pattern (ref) (n=295)	Mixed pattern (n=940)	Prudent pattern (n=252)	N
Daytime sleepiness				
Model 1 [2]	1.00	0.95 (0.78 - 1.17)	0.78 (0.59 - 1.02)	1,487
Model 2 [3]	1.00	0.94 (0.75 - 1.19)	0.80 (0.59 - 1.09)	1,255
Model 3 [4]	1.00	0.96 (0.77 - 1.21)	0.83 (0.61 - 1.13)	1,255
Model 4 [5]	1.00	0.97 (0.77 - 1.22)	0.86 (0.63 - 1.17)	1,220
Poor sleep quality [6]				
Model 1 [2]	1.00	0.94 (0.71 - 1.23)	0.79 (0.54 - 1.15)	751
Model 2 [3]	1.00	1.00 (0.73 - 1.37)	0.85 (0.55 - 1.30)	620
Model 3 [4]	1.00	1.01 (0.73 - 1.38)	0.86 (0.56 - 1.32)	620
Model 4 [5]	1.00	1.03 (0.75 - 1.42)	0.94 (0.61 - 1.47)	601

[1] Poisson regression was performed for the association between dietary patterns and self-reported sleep outcomes.
[2] Model 1 adjusted for age.
[3] Model 2 further adjusted for education, smoking, alcohol, physical activity and shift work.
[4] Model 3 further adjusted for waist circumference.
[5] Model 4 further adjusted for depression, diabetes and medication.
[6] Poor sleep quality was measured in MAILES participants who participated polysomnography, the number of participants in each pattern refers to the numbers for polysomnography measured in Table 5.

Table 5. 4 Associations between dietary patterns and PSG sleep outcomes [1]

PSG sleep parameters	Western pattern (ref) (n=145)	Mixed pattern (n=509)	Prudent pattern (n=130)	N
Sleep onset latency (min)				
Model 1 [2]	0	-3.27 (-6.83, 0.29)	-6.20 (-10.83, -1.56)**	784
Model 2 [3]	0	-4.02 (-8.03, -0.00)*	-6.12 (-11.32, -0.92)*	650
Model 3 [4]	0	-4.09 (-8.11, 0.06)	-6.25 (-11.47, -1.04)*	650
Model 4 [5]	0	-4.34 (-8.34, -0.34)*	-6.34 (-11.57, -1.11)*	630
Apnoea hypopnea index (/hour)				
Model 1 [2]	0	-2.14 (-4.71, 0.43)	-2.54 (-5.89, 0.81)	784
Model 2 [3]	0	-2.33 (-5.23, 0.57)	-1.82 (-5.58, 1.93)	650
Model 3 [4]	0	-1.80 (-4.60, 1.01)	-0.82 (-4.46, 2.82)	650
Model 4 [5]	0	-2.14 (-4.71, 0.43)	-2.54 (-5.89, 0.81)	630
Total sleep duration (min)				
Model 1 [2]	0	1.61 (-9.14, 12.4)	2.41 (-11.6, 16.4)	784
Model 2 [3]	0	-1.56 (-13.9, 10.7)	-4.88 (-20.8, 11.0)	650
Model 3 [4]	0	-1.81(-14.1, 10.5)	-5.34 (-21.3, 10.6)	650
Model 4 [5]	0	-2.26 (-14.7, 10.2)	-4.63 (-21.0, 11.7)	630

[1] Coefficients (95% CI) were presented from multivariable linear regression models.
[2] Model 1 adjusted for age.
[3] Model 2 extra adjusted for education, smoking, alcohol, physical activity and shift work.
[4] Model 3 extra adjusted for waist circumference.
[5] Model 4 extra adjusted for depression, diabetes and medication. **p<0.01, *P<0.05

Supplemental Table 5. 1. Food intakes (in food groups) across quartiles of factor 1 and factor 2 according to factor analysis

a) Factor1 (food groups were ordered by factor scores in factor 1 from high to low)

	Factor 1				
Food groups (g)	Q1	Q2	Q3	Q4	p-value [1]
Root vegetables, mean (SD)	7.7 (6.4)	12.5 (9.4)	19.1 (12.3)	34.1 (19.5)	<0.001
Stalk vegetables, mean (SD)	3.9 (3.5)	7.0 (5.7)	9.9 (6.9)	16.6 (10.6)	<0.001
Cabbages, mean (SD)	14.2 (12.2)	20.9 (17.7)	33.5 (24.0)	54.6 (37.3)	<0.001
Other fruit, mean (SD)	130 (84.4)	204 (138)	264 (160)	360 (211)	<0.001
Fruity vegetables, mean (SD)	72.7 (70.1)	116 (85.6)	163 (116.4)	234 (161.4)	<0.001
Leafy vegetables, mean (SD)	10.4 (12.1)	18.2 (15.0)	28.1 (25.8)	45.8 (37.9)	<0.001
Potatoes without fat, mean (SD)	9.7 (12.3)	14.6 (15.7)	21.4 (23.0)	34.7 (31.8)	<0.001
Legumes, mean (SD)	26.5 (27.5)	39.0 (36.9)	51.7 (42.7)	71.6 (61.2)	<0.001
High fibre bread, mean (SD)	29.0 (40.5)	53.6 (45.0)	62.2 (48.0)	76.3 (51.9)	<0.001
Nuts, mean (SD)	2.8 (4.7)	5.0 (7.0)	7.2 (10.3)	11.4 (14.6)	<0.001
Citrus fruit, mean (SD)	8.5 (12.9)	13.8 (21.8)	20.8 (29.2)	31.1 (37.1)	<0.001
Other cereal, mean (SD)	37.3 (49.2)	56.1 (60.4)	67.7 (65.1)	91.6 (76.9)	<0.001
Fish, mean (SD)	14.0 (18.6)	23.9 (26.1)	29.0 (28.9)	37.8 (41.2)	<0.001
Tea, mean (SD)	203 (320)	276 (330)	333 (349)	480 (417)	<0.001
Jam vegemite, mean (SD)	5.8 (6.7)	8.4 (9.7)	9.1 (8.6)	12.4 (13.4)	<0.001
Medium fat dairy, mean (SD)	64.5 (134)	114.8 (182)	162.2 (227)	182.3 (219)	<0.001
Dressing, mean (SD)	9.4 (9.4)	12.4 (11.2)	13.5 (10.3)	14.5 (12.7)	<0.001

Juices, mean (SD)	62.7 (91.8)	88.6 (126)	115.7 (144)	133.3 (185)	<0.001
Skim milk, mean (SD)	34.6 (103)	92.0 (176)	109.7 (201)	115.4 (197)	<0.001
Other bread, mean (SD)	0.9 (6.4)	2.2 (9.9)	3.5 (13.1)	6.2 (19.3)	<0.001
Peanut butter, mean (SD)	6.2 (11.6)	6.4 (9.8)	9.0 (16.4)	10.1 (15.1)	<0.001
Eggs, mean (SD)	21.8 (17.5)	23.0 (16.9)	24.4 (17.4)	26.4 (20.4)	<0.001
High fibre cereal, mean (SD)	1.8 (7.1)	3.3 (9.4)	4.0 (11.1)	4.3 (10.7)	<0.001
Wine, mean (SD)	55.7 (115)	87.8 (167)	98.3 (198)	91.0 (147)	<0.001
Red meat, mean (SD)	87.2 (74.0)	82.6 (57.5)	87.6 (53.5)	93.6 (81.9)	0.11
Pasta/noodle and rice, mean (SD)	45.4 (55.2)	51.6 (47.5)	52.7 (45.6)	50.5 (47.2)	0.11
Tomato sauce, mean (SD)	7.1 (10.4)	7.1 (10.3)	7.9 (11.3)	7.6 (11.5)	0.64
Potatoes with fat, mean (SD)	8.4 (13.7)	9.2 (14.8)	10.1 (13.9)	9.3 (14.0)	0.36
Poultry, mean (SD)	38.6 (37.6)	39.8 (33.1)	37.6 (23.2)	42.5 (40.8)	0.17
Snacks, mean (SD)	86.1 (76.1)	80.0 (58.5)	79.0 (56.8)	81.7 (60.1)	0.35
Spread, mean (SD)	20.3 (19.2)	17.5 (15.7)	18.3 (16.5)	19.0 (17.2)	0.09
Cooking oil, mean (SD)	9.1 (9.3)	8.2 (8.9)	7.9 (9.2)	8.1 (9.3)	0.16
Take away foods, mean (SD)	21.1 (16.9)	19.6 (16.8)	21.0 (21.2)	17.5 (26.0)	0.03
Coffee, mean (SD)	430 (366)	428 (328)	383 (310)	355 (311)	<0.001
Flavoured milk, mean (SD)	19.3 (82.6)	11.0 (58.7)	5.2 (35.1)	6.5 (39.6)	<0.001
Processed meat, mean (SD)	34.4 (33.3)	31.4 (24.8)	31.2 (23.4)	28.2 (24.8)	0.008
Spirits, mean (SD)	39.3 (145)	21.2 (69.9)	18.0 (74.7)	5.6 (20.0)	<0.001
Beer, mean (SD)	363 (629)	286 (491)	221 (369)	173 (314)	<0.001

High fat dairy, mean (SD)	183 (222)	129 (193)	92.2 (154)	74.4 (147)	<0.001
Soft drinks, mean (SD)	412 (513)	246 (316)	201 (258)	164 (237)	<0.001
White bread, mean (SD)	49.8 (56.0)	23.8 (41.3)	15.2 (31.5)	9.7 (24.5)	<0.001

[1] p values were from ANOVA analysis unadjusted

b) Factor 2 (food groups were ordered by factor scores in factor 2 from high to low)

	Factor 2				
Food groups (g)	Q1	Q2	Q3	Q4	p-value†
Processed meat, mean (SD)	14.9 (13.2)	25.0 (16.6)	34.6 (20.8)	50.8 (36.4)	<0.001
Snacks, mean (SD)	46.0 (34.4)	66.0 (39.2)	86.1 (49.3)	129 (84.8)	<0.001
Tomato sauce, mean (SD)	3.0 (4.8)	4.4 (5.6)	7.2 (7.8)	15.1 (16.5)	<0.001
Red meat, mean (SD)	55.5 (39.9)	80.7 (47.6)	90.8 (47.6)	124 (99.3)	<0.001
Take away foods, mean (SD)	12.6 (11.0)	16.9 (12.4)	20.7 (15.1)	29.1 (32.4)	<0.001
Spread, mean (SD)	10.8 (11.2)	16.0 (13.4)	20.7 (16.6)	27.7 (21.3)	<0.001
Poultry, mean (SD)	27.5 (21.9)	36.7 (24.0)	41.8 (25.3)	52.6 (52.1)	<0.001
Jam vegemite, mean (SD)	4.8 (6.3)	7.1 (7.4)	9.8 (9.7)	13.9 (13.4)	<0.001
Fruity vegetables, mean (SD)	101 (78.2)	136 (97.2)	147 (101)	203 (187)	<0.001
White bread, mean (SD)	9.8 (24.4)	15.7 (30.6)	27.7 (42.2)	45.5 (57.8)	<0.001
Potatoes with fat, mean (SD)	4.9 (7.7)	7.9 (13.3)	10.3 (14.4)	13.9 (17.5)	<0.001
Soft drinks, mean (SD)	152 (198)	215 (315)	251 (331)	405 (489)	<0.001
Beer, mean (SD)	158 (311)	200 (356)	242 (400)	443 (679)	<0.001
Juices, mean (SD)	56.6 (83.9)	88.9 (121)	110 (157)	145 (178)	<0.001
Eggs, mean (SD)	20.2 (15.6)	21.6 (16.2)	23.2 (17.1)	30.6 (21.5)	<0.001
Pasta/noodle and rice, mean (SD)	37.0 (40.7)	49.5 (48.0)	52.3 (42.3)	61.5 (60.0)	<0.001
Other fruit, mean (SD)	205 (142)	234 (168)	241 (173)	278 (209)	<0.001
Peanut butter, mean (SD)	5.2 (10.9)	6.9 (10.4)	8.6 (15.8)	11.0 (15.7)	<0.001

High fat dairy, mean (SD)	84.3 (150)	100 (172)	131 (183)	164 (222)	<0.001
Cabbages, mean (SD)	24.3 (25.2)	29.9 (26.9)	32.9 (29.9)	36.1 (32.5)	<0.001
Cooking oil, mean (SD)	6.7 (8.2)	7.7 (7.8)	8.5 (8.9)	10.3 (11.1)	<0.001
Coffee, mean (SD)	312 (293)	388 (300)	439 (339)	459 (367)	<0.001
Root vegetables, mean (SD)	14.4 (12.9)	17.7 (14.4)	20.1 (17.8)	21.3 (18.4)	<0.001
Fish, mean (SD)	22.2 (23.8)	26.0 (27.9)	26.2 (29.5)	30.4 (40.1)	0.001
Dressing, mean (SD)	11.2 (10.0)	11.6 (9.5)	12.5 (11.1)	14.5 (13.2)	<0.001
Leafy vegetables, mean (SD)	19.3 (21.5)	26.2 (28.2)	27.4 (29.1)	29.6 (31.8)	<0.001
Legumes, mean (SD)	41.6 (41.7)	44.4 (44.2)	50.0 (47.2)	52.7 (53.0)	0.001
Spirits, mean (SD)	10.3 (35.5)	13.1 (47.9)	24.1 (84.7)	36.7 (146)	<0.001
High fibre bread, mean (SD)	49.3 (44.5)	55.8 (45.1)	56.3 (48.7)	59.7 (58.3)	0.016
Stalk vegetables, mean (SD)	8.1 (8.3)	9.4 (8.6)	9.5 (8.3)	10.5 (9.0)	<0.001
Potatoes without fat, mean (SD)	17.6 (23.0)	20.1 (24.4)	21.0 (23.5)	21.6 (24.6)	0.06
Flavoured milk, mean (SD)	7.6 (48.1)	12.0 (65.6)	14.4 (65.6)	8.1 (47.4)	0.22
Other bread, mean (SD)	3.0 (11.8)	2.2 (9.3)	4.7 (17.7)	2.9 (12.4)	0.035
Wine, mean (SD)	80.2 (139)	86.1 (166)	93.0 (197)	73.6 (131)	0.31
High fibre cereal, mean (SD)	3.3 (10.0)	3.9 (10.5)	3.3 (9.5)	2.9 (8.9)	0.45
Skim milk, mean (SD)	97.4 (181)	98.7 (186)	76.6 (163)	78.8 (175)	0.11
Citrus fruit, mean (SD)	20.6 (33.6)	19.9 (28.1)	15.4 (23.5)	18.2 (25.8)	0.027
Medium fat dairy, mean (SD)	137 (210)	144 (197)	136 (211)	107 (175)	0.026
Nuts, mean (SD)	7.1 (12.7)	6.9 (10.9)	6.7 (9.5)	5.5 (7.8)	0.10

Tea, mean (SD)	400 (420)	309 (335)	294 (357)	289 (352)	<0.001
Other cereal, mean (SD)	78.8 (79.3)	64.9 (64.6)	61.2 (61.2)	47.8 (55.5)	<0.001

[1] p values were from ANOVA analysis unadjusted

Supplemental Table 5. 2 Food intakes (in food groups) across the three patterns (western, mixed and prudent) that based on the distribution of two factors.

Food groups	Western pattern	Mixed pattern	Prudent pattern	p-value [1]
High fat dairy, mean (SD)	202 (228)	114 (180)	50.3 (104)	<0.001
Medium fat dairy, mean (SD)	63.1 (124)	140 (207)	174 (219)	<0.001
Skim milk, mean (SD)	45.4 (125)	87.9 (176)	135 (211)	<0.001
Flavoured milk, mean (SD)	15.8 (68.3)	10.4 (58.3)	5.2 (36.5)	0.060
Juices, mean (SD)	92.4 (117)	106 (156)	85.7 (115)	0.044
Soft drinks, mean (SD)	476 (557)	229 (287)	109 (174)	<0.001
Tea, mean (SD)	213 (326)	307 (347)	503 (430)	<0.001
Coffee, mean (SD)	468 (374)	409 (326)	287 (261)	<0.001
Red meat, mean (SD)	111 (82.9)	85.7 (66.1)	69.0 (43.9)	<0.001
Processed meat, mean (SD)	48.5 (37.2)	30.2 (22.7)	16.3 (14.9)	<0.001
Poultry, mean (SD)	50.0 (46.7)	38.3 (31.5)	33.1 (24.4)	<0.001
Fish, mean (SD)	18.6 (22.6)	27.1 (33.0)	31.4 (30.1)	<0.001
Take away foods, mean (SD)	26.2 (20.7)	19.9 (21.8)	12.3 (11.6)	<0.001
Pasta rice, mean (SD)	55.7 (60.6)	50.4 (46.8)	42.6 (41.6)	0.003

High fibre cereal, mean (SD)	2.0 (7.8)	3.5 (9.8)	4.3 (11.0)	0.006
Other cereal, mean (SD)	37.5 (47.7)	59.8 (61.8)	104 (82.0)	<0.001
Potatoes with fat, mean (SD)	10.8 (14.3)	9.9 (15.1)	5.1 (7.3)	<0.001
Potatoes without fat, mean (SD)	12.8 (14.1)	19.5 (23.4)	30.3 (30.3)	<0.001
Citrus fruit, mean (SD)	9.5 (15.9)	17.8 (25.1)	31.3 (41.4)	<0.001
Other fruit, mean (SD)	174 (135)	243 (182)	300 (172)	<0.001
Fruity vegetables, mean (SD)	112 (102)	151 (141)	169 (98.2)	<0.001
Stalk vegetables, mean (SD)	5.7 (5.3)	9.3 (8.3)	13.9 (10.3)	<0.001
Root vegetables, mean (SD)	11.2 (9.6)	18.4 (16.9)	26.3 (15.9)	<0.001
Cabbages, mean (SD)	18.8 (16.4)	31.2 (29.4)	42.7 (33.3)	<0.001
Leafy vegetables, mean (SD)	14.1 (14.4)	26.6 (29.1)	35.0 (31.9)	<0.001
Legumes, mean (SD)	34.3 (34.5)	47.3 (47.4)	61.0 (52.7)	<0.001
High fibre bread, mean (SD)	36.8 (48.2)	58.6 (49.2)	63.3 (47.8)	<0.001
White bread, mean (SD)	62.9 (60.7)	18.7 (33.9)	4.2 (13.9)	<0.001
Other bread, mean (SD)	1.2 (6.9)	3.5 (14.1)	4.4 (14.8)	0.004
Eggs, mean (SD)	26.1 (19.9)	23.8 (17.9)	21.8 (17.0)	0.009
Spread, mean (SD)	26.0 (20.8)	18.5 (16.3)	11.9 (12.5)	<0.001

Beer, mean (SD)	460 (740)	243 (394)	102 (202)	<0.001
Wine, mean (SD)	59.6 (120)	89.6 (178)	85.9 (122)	0.009
Spirits, mean (SD)	50.0 (169)	16.8 (61.4)	4.7 (17.9)	<0.001
Snacks, mean (SD)	116 (84.8)	79.3 (55.9)	52.3 (40.0)	<0.001
Nuts, mean (SD)	3.4 (5.1)	6.2 (9.0)	11.6 (16.1)	<0.001
Peanut butter, mean (SD)	8.7 (13.5)	7.8 (13.7)	7.8 (13.5)	0.54
Jam vegemite, mean (SD)	9.7 (10.6)	9.2 (10.5)	6.9 (8.0)	<0.001
Tomato sauce, mean (SD)	11.8 (14.0)	7.2 (10.5)	3.6 (5.6)	<0.001
Dressing, mean (SD)	11.1 (10.5)	13.0 (11.6)	12.0 (9.7)	0.017
Cooking oil, mean (SD)	9.7 (9.8)	8.4 (9.3)	6.4 (7.6)	<0.001

[1] p values were from ANOVA analysis unadjusted

Supplemental Table 5. 3 Associations between quartiles of separate factors from factor analysis and PSG sleep parameters [1]

	Factor 1					Factor 2				
	β (95% CI)					β (95% CI)				
	Q1(ref)	Q2	Q3	Q4	P for trend[2]	Q1(ref)	Q2	Q3	Q4	p for trend[2]
Sleep onset latency (min)										
Model1 [3]	0	-4.67 (-8.50, -0.84)*	-4.22 (-8.03, -0.40)*	-6.27 (-10.1, -2.44)**	0.003	0	0.86 (-2.97, 4.69)	2.08 (-1.76, 5.92)	0.20 (-3.67, 4.08)	0.93
Model2 [4]	0	-5.17 (-9.43, -0.91)*	-5.72 (-10.0, -1.43)**	-6.41 (-10.8, -2.01)**	0.008	0	1.71 (-2.45, 5.88)	2.71 (-1.50, 6.92)	-0.10 (-4.34, 4.13)	0.78
Model3 [5]	0	-5.20 (-9.46, -0.93)*	-5.76 (-10.1, -1.46)**	-6.48 (-10.9, -2.07)**	0.008	0	1.80 (-2.38, 5.98)	2.75 (-1.47, 6.96)	-0.03 (-4.24, 4.30)	0.81
Model4 [6]	0	-3.63 (-7.92, 0.65)	-4.94 (-9.22, -0.67)*	-5.44 (-9.87, -1.00)*	0.018	0	2.34 (-1.86, 6.54)	3.00 (-1.19, 7.20)	0.60 (-3.70, 4.90)	0.97
Apnoea-hypopnea index (/hour)										
Model1 [3]	0	-1.75 (-4.50, 1.00)	-1.76 (-4.50, 0.98)	0.77 (-1.99, 3.52)	0.45	0	-1.02 (-3.77, 1.74)	1.01 (-1.76, 3.77)	3.26 (0.47, 6.04)*	0.002
Model2 [4]	0	-3.75 (-6.81, -0.69)*	-3.18 (-6.26, -0.10)*	-0.58 (-3.73, 2.58)	0.77	0	-0.99 (-3.98, 2.00)	-0.13 (-3.15, 2.90)	2.62 (-0.42, 5.66)	0.023
Model3 [5]	0	-3.52 (-6.47, -0.56)*	-2.90 (-5.88, -0.07)*	-0.01 (-3.04, 3.07)	0.53	0	-1.78 (-4.67, 1.12)	-0.44 (-3.35, 2.48)	1.47 (-1.49, 4.42)	0.08
Model4 [6]	0	-3.18 (-6.20, -0.16)*	-2.96 (-5.98, 0.06)	0.05 (-3.08, 3.18)	0.62	0	-2.34 (-5.30, 0.62)	-1.01 (-3.97, 1.95)	1.13 (-1.90, 4.16)	0.11
Total sleep duration (min)										

Model1 [3]	0	-4.39 (-16.0, 7.19)	-3.48 (-15.0, 8.05)	1.25 (-10.4, 12.9)	0.80	0	2.20 (-9.39, 13.8)	-0.61 (-12.2, 11.0)	-7.51 (-19.2, 4.21)	0.17
Model2 [4]	0	-6.59 (-19.7, 6.48)	-6.93 (-20.1, 6.24)	-1.53 (-15.0, 12.0)	0.87	0	4.59 (-8.19, 17.4)	2.45 (-10.5, 15.4)	-3.92 (-16.9, 9.08)	0.45
Model3 [5]	0	-6.68 (-19.8, 6.40)	-7.04 (-20.2, 6.14)	-1.77 (-15.3, 11.8)	0.85	0	4.90 (-7.92, 17.7)	2.57 (-10.4, 15.5)	-3.46 (-16.5, 9.63)	0.49
Model4 [6]	0	-9.12 (-22.5, 4.25)	-8.13 (-21.5, 5.22)	-3.59 (-17.4, 10.3)	0.70	0	5.06 (-8.05, 18.2)	1.60 (-11.5, 14.7)	-3.88 (-17.3, 9.54)	0.46

[1] Results presented were from multivariable linear regression models.
[2] p for trend was calculated using the median value of the factor score by the quartiles of scores of the factor.
[3] Model 1 adjusted for age.
[4] Model 2 extra adjusted for education, smoking, alcohol, physical activity and shift work.
[5] Model 3 extra adjusted for waist circumference.
[6] Model 4 extra adjusted for depression, diabetes and medication.
**p<0.01, *p<0.05

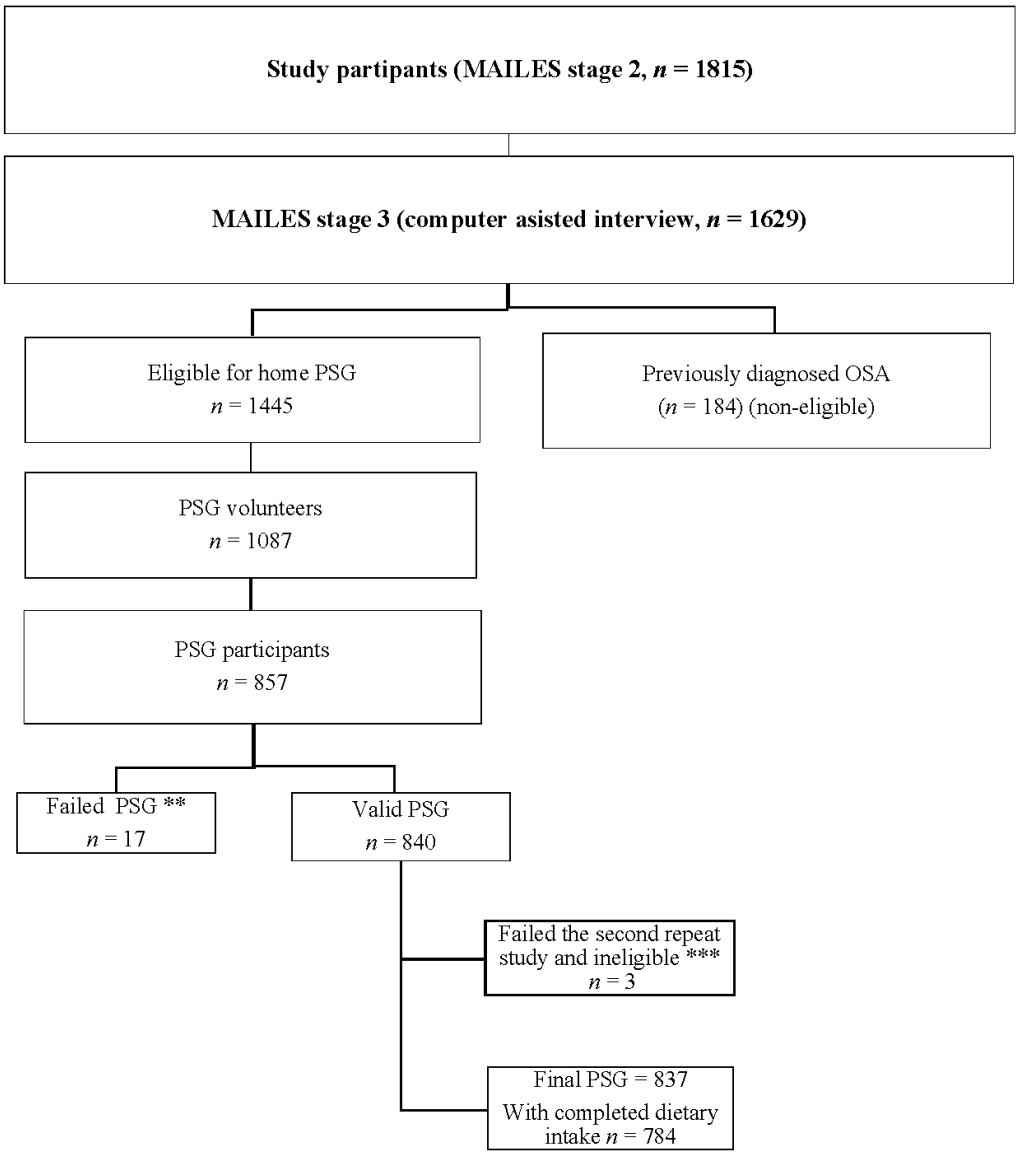

Figure 5. 1 The flow chart of study participants with dietary intake (MAILES stage 2) and MAILES stage 3 with PSG recruitment

* n = 17 failed and did not repeat the study (n = 15 TST was not ≥3.5 hours from ≥5 hours recording; n = 1 poor respiratory signals; n = 1 poor EEG);

** n = 2 TST was not ≥3.5 hours from ≥5 hours recording, and n = 1 subsequently found to be ineligible [155].

PSG, polysomnography. EEG Electroencephalogram. TST, total sleep time. Electroencephalogram.

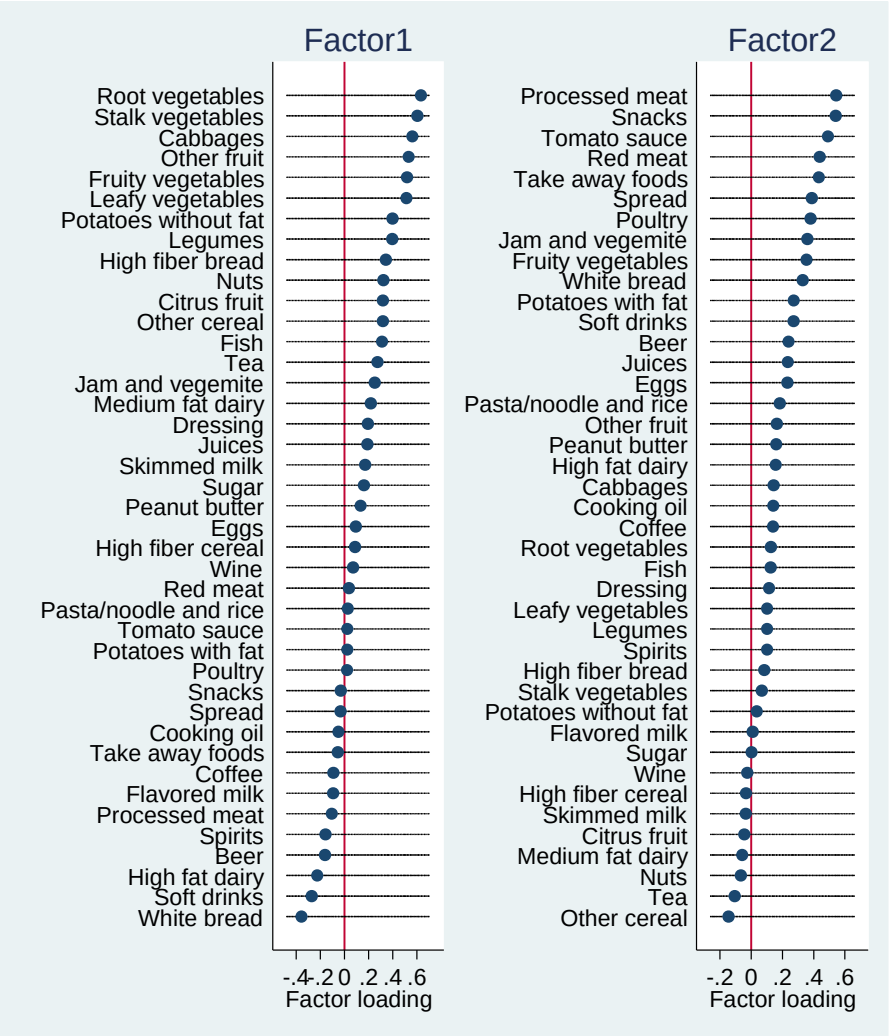

Figure 5. 2 Factor loadings of two factors

CHAPTER 6 NUTRIENT PATTERNS AND CHRONIC INFLAMMATION/ SLEEP OUTCOMES

6.1 Publication

Cao Y, Wittert G, Taylor AW, Adams R, Shi, Z. Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men. Clinical Nutrition, 2016, doi: 10.1016/j.clnu.2016.06.018

Statement of Authorship

Title of Paper	Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Cao, Y., Wittert, G., Taylor, A. W., Adams, R., Appleton, S., & Shi, Z. (2016). Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men. Clinical Nutrition. doi: 10.1016/j.clnu.2016.06.018

Principal Author

Name of Principal Author (Candidate)	Yingting Cao
Contribution to the Paper	Conception and design, statistical analysis, interpretation of data, manuscript preparation, and critical revision of the manuscript.
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 26/10/2016

Co-Author Contributions

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

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

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

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

Name of Co-Author	Gary Wittert
Contribution to the Paper	Conception and design, interpretation of results, critical manuscript evaluation and editing. Contribution to the materials/analysis tools.
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Contribution to the Paper	Contribution to the conception and design of the study. Critical manuscript evaluation and editing. Contribution to the materials/analysis tools.
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Name of Co-Author	Robert Adams
Contribution to the Paper	Conception, interpretation of the results, contributions to the sleep study, interpretation of the results and critical revision of the manuscript.
Signature	Date 27/10/2016

Name of Co-Author	Sarah Appleton
Contribution to the Paper	Conception, interpretation of the results, contributions to the sleep study, interpretation of the results and critical revision of the manuscript.
Signature	Date 26/10/2016

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Contribution to the Paper	Supervised the development of the work. Conception and design, interpretation of the results and critical revision of the manuscript. Statistical assistance and contribution to the materials/analysis tools.
Signature	Date 26/10/2016

Clinical Nutrition xxx (2016) 1–8

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men

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ARTICLE INFO

Article history:
Received 16 April 2016
Accepted 27 June 2016

Keywords:
Nutrient patterns
Inflammation
Apnoea-hypopnoea index
C-reactive protein
Lifestyle

SUMMARY

Background & aims: There is limited data relating to the effect of the combination of nutrients on inflammation and the interactions with lifestyle factors and chronic conditions. We examined the association between nutrient patterns and inflammatory markers C-reactive protein (CRP) and interleukin 6 (IL-6) in community dwelling middle-aged and elderly Australian men.

Methods: Participants (mean age 59.7 y) with complete data relating to diet and fasting serum inflammatory markers in the Men Androgen Inflammation Lifestyle Environment and Stress cohort were analysed (n = 1577 for CRP, n = 1557 for IL-6). Food intake was assessed using a food frequency questionnaire, and nutrient patterns were identified by factor analysis. Biomedical examinations were conducted in The Queen Elizabeth Hospital and Lyell McEwin Health Service. CRP and IL-6 were log transformed due to the skewed distribution. Linear regression models were used to assess the association between nutrient patterns and inflammation.

Results: We generated three nutrient patterns by factor analysis. An animal-sourced pattern (animal protein, cobalamin, cholesterol and omega-6) was positively associated with CRP (p for trend across quartiles 0.057). A plant-sourced pattern (beta-carotene, vitamin A, lutein and zeaxanthin) was inversely associated with CRP (p for trend across quartiles 0.005). The association between plant-sourced pattern and CRP was stronger in participants with severe sleep apnoea, smoking (p for interaction 0.019), and participants without diabetes (p for interaction 0.238) and/or with normal triglycerides (p for interaction 0.005) and high density lipoprotein (p for interaction 0.120) compared with their counterparts. No interactions were found between the animal-sourced pattern and lifestyle factors and chronic conditions. No independent associations were found between the animal/plant-sourced pattern and IL-6. No associations were found between the vitamin B and folate pattern (total folate, thiamine, riboflavin and niacin) and inflammatory markers.

Conclusions: While an animal-sourced pattern may enhance inflammation level, a plant-sourced pattern may reduce inflammation particularly in people with less healthy lifestyles and severe obstructive apnoea.

1. Introduction

A number of chronic diseases, including obesity [1], type 2 diabetes [2], cardiovascular diseases [3] and obstructive sleep apnoea (OSA) [4] are associated with inflammation. Lifestyle factors including smoking [5] and physical inactivity [6] increase inflammatory burden. Diet can modulate inflammation by suppressing or triggering pro-inflammatory markers [7]. Fibre, ω-3 polyunsaturated fatty acids, fruits and vegetables have anti-inflammatory effects; saturated fatty acids and trans-fatty acids are pro-inflammatory [8].

Studies on dietary patterns show that the Mediterranean pattern or a 'healthy' pattern characterised by vegetables, fruits, nuts and grains are anti-inflammatory, while a 'Western-like'

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http://dx.doi.org/10.1016/j.clnu.2016.06.018
0261-5614/

pattern that is characterised by red and processed meat and snacks is pro-inflammatory [8,9]. Studies on the interactions between inflammation and chronic diseases and how they are modified by diets have shown inconsistent results. For example, in a randomized controlled trial, a diet low in saturated fat and high in fibre, plant sterols and grains reduced CRP levels in hyperlipidemic patients compared with controls [10]. Mediterranean diets have been shown to reduce inflammation in a randomized controlled trial for 12 months in patients with diabetes, or with three or more major cardiovascular risks (hypertension, obesity, dyslipidaemia etc.) [11], but have failed to reduce inflammatory markers in patients with coronary artery disease in another one year randomized controlled trial [12].

An alternative approach to evaluate dietary effects is to examine the combination of nutrients and generate nutrient patterns. Compared with dietary patterns, nutrient patterns provide an easier way to compare between populations because no matter what foods were consumed, the component nutrients in foods remained the same [13]. Among the existing studies that investigated the combination of nutrients, most focused on cancer patients [14,15], one focused on obesity [16], and few have examined the association with inflammation.

In the current study, we aimed to 1) examine the association between nutrient patterns and CRP and IL-6 levels in community middle-aged and elderly men in South Australia; 2) examine if the associations between nutrient patterns and inflammatory markers are modified by factors including lifestyles, OSA and other chronic conditions.

2. Methods

2.1. Study population

We used data from the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) cohort study, which has been described in detail previously [17]. In brief, MAILES is the harmonisation of two ongoing prospectively followed cohorts: eligible male participants from the North West Adelaide Health Study (NWHAS) [18] and all participants from the Florey Adelaide Male Ageing Study (FAMAS) [19]. MAILES stage 1 (baseline) contained participants from NWHAS at the first follow-up clinic visit (2004–2006) and participants from FAMAS at the baseline clinic visit (2002–2005) as well as a computer assisted telephone interview (CATI)/questionnaire. MAILES stage 2 occurred approximately five years after MAILES stage 1 assessments for both cohorts, and included CATI and administration of questionnaires. MAILES stage 3 was a joint follow up using CATI and questionnaire conducted in 2010–2011. Participants were recruited using the telephone to conduct interviewers and the Electronic White Pages as the sampling frame. Residential households were selected at random by a computer and randomly selection was also conducted within the household for both cohorts for interview and clinic visits [20,21]. This method of randomly selecting within the household avoids selection bias towards unemployed and retired or housewives, as those most likely to be at home when the initial call was made [22]. The general inclusion criterion were: 1) male and aged 35–80 years at the time of recruitment; 2) household with a telephone connected and telephone number listed in the Electronic White Pages. The exclusion criterion were: 1) non-English speaking; 2) mental or physical illness that disables the communication ability; 3) too ill or otherwise incapacitated to attend clinics; 4) current residence in an aged care facility. In this study, we included 1815 men with completed dietary intake from MAILES stage 2 (2007–2010), among whom, 1586 had CRP measurements and 1557 had IL-6 measurements (Fig. 1). We excluded those with

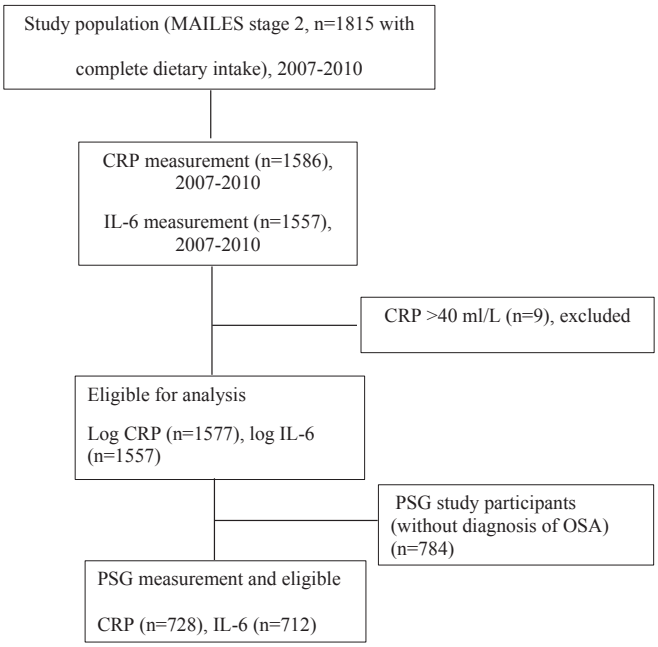

Fig. 1. Flow chart of study population.

CRP higher than 40 ml/L (n = 9) as it is suggestive of an acute infection or inflammatory disease [23]. In MAILES stage 3, polysomnography (PSG) was conducted in men identified by the CATI to be without a previous diagnosis of OSA assessed by an overnight sleep study (included in the current study n = 728). Ethics approval was obtained from the Queen Elizabeth Hospital Human Ethics Committee (number 2010054) and the Royal Adelaide Hospital Human Research Ethics Committee (number 020305h).

2.2. Dietary intake assessment

Dietary intake was measured by the Cancer Council Victoria Diet Questionnaire for Epidemiological Studies (DQES-V3.1 (FFQ)). The FFQ has been validated in an Australian population and is widely used in epidemiological studies [24]. The questionnaire asks the participant's habitual consumption of 167 foods and six alcohol beverages over the last 12-month on a 10-point frequency scale. Additional questions were asked about the use of bread, dairy products and fat spreads. Nutrient intakes were computed from the dietary data by the means of the nutrient composition tables in the NUTTAB95 database (Food Standards Australia New Zealand, Canberra, 1995). Nutrients intake from supplements were not included in the analysis because the information collected was not sufficiently detailed to calculate (by Cancer Council Victoria).

2.3. Measurement of CRP and IL-6 and other biomarkers

Biomarkers analysed in the study were from the fasting blood samples drawn during morning clinic visits in hospital-based clinics (The Queen Elizabeth Hospital and Lyell McEwin Health Service) at MAILES stage 2. Blood samples were stored on ice 0.5–3.5 h before being transported for immediate laboratory analysis. Plasma and sera from blood samples were frozen at −70 °C and thawed for subsequent analysis of inflammatory markers [20]. Clinic visit appointments were re-scheduled if participants were acutely unwell. Serum levels of high-sensitivity CRP and IL-6 were quantitated with an enzyme linked immunosorbent assay (ELISA) and Cobas auto analyser (Roche Diagnostics, Florham Park, New

Please cite this article in press as: Cao Y, et al., Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.06.018

Jersey, US). The inter-assay coefficients of variation were 2.1 for high-sensitivity CRP and 7.8 for IL-6 [17]. Other biomarkers such as insulin (Abbott Architect immunoassay analyser (Abbott Park, IL USA)), glucose (Olympus AU5400 (Olympus Optical C Lid, Japan)), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (Olympus AU5400 (Olympus Optical C Lid, Japan)) were also measured.

2.4. Sleep apnoea assessment

In men without a prior diagnosis of OSA (n = 784), apnoea-hypopnoea index (AHI) was assessed as previously described [25] by a single overnight 8-channel in-home PSG (Embletta X100 (http://www.embla.com/index.cfm/id/57/Embletta-X100/)) which also measured electroencephalography, electrooculography, electromyography, electrocardiograms, thoracic and abdominal bands for respiratory effort, nasal pressure cannula for nasal airflow, body position and oximetry. AHI was computed as the sum of respiratory events (apneas and hypopneas) divided by hours slept. AHI severity was categorised as follows: <5/hour, 5–19/hour and ≥20/hour.

2.5. Other measurements

Other measurements such as anthropometric values and blood pressure were measured by trained clinic staff during clinic visits. Lifestyle variables including physical activity, smoking and alcohol consumption as well as demographic, psychosocial, and economic factors (questionnaire) were also collected at MAILES 2 using a validated questionnaire [17]. Body weight was measured in light indoor clothing without shoes to the nearest 100 g. Height was measured without shoes to the nearest mm using a stadiometer. Waist circumference was measured to the nearest mm midway between the inferior margin of the last rib and the crest of the ilium, in the mid-axillary line in a horizontal plane. Blood pressure was measured twice by mercury sphygmomanometer on the right upper arm of the subject, who was seated and relaxed for 5 min before the measurement.

2.6. Statistical analysis

2.6.1. Identification of nutrient patterns

Nutrient patterns were identified by factor analysis using 34 nutrients that were summarised from all measured nutrients as input variables. Alcohol consumption was considered as a lifestyle factor and was adjusted as a covariate, therefore was not included in the nutrient patterns. Varimax rotation was used to improve interpretability and minimize the correlation between the factors. The final number of nutrient patterns was determined by eigenvalue >1, scree plot, and interpretability of the factors. Factor loadings for each nutrient were calculated and factor scores for each pattern were calculated for each participant by summing the total grams of the 34 types of nutrients weighted by their factor loadings. Nutrient patterns were named according to the nutrient groups loading highest on each of the factors.

2.6.2. Data analyses

Factor scores of nutrient patterns were recoded into quartiles. Chi square test was used to compare difference between categorical variables and ANOVA was used to compare differences in continuous variables between nutrient patterns in demographic characteristics. Linear regression analyses were used to test the association between nutrient pattern scores (continuous variable) and CRP and IL-6. CRP and IL-6 was log transformed due to the skewed distribution. A set of multivariable models were used: model 1 adjusted for age; model 2 further adjusted for education, smoking, sedentary lifestyle, and shift-work; model 3 further adjusted for waist circumference as visceral adiposity was more etiologically related to inflammation; model 4 further adjusted for chronic diseases related markers including fasting glucose, LDL cholesterol, HDL cholesterol and systolic blood pressure. Subgroup analysis was graphically presented using user written command 'ipdover'. Interactions between nutrient patterns and OSA, as well as lifestyle factors and chronic conditions were conducted by adding a multiplicative term with lifestyle factors and chronic conditions as categorical variables and the dichotomised factor score of nutrient patterns in the model. Sensitivity analyses were performed to test the robustness of the results. Firstly, we tested whether the interactions were affected by medication by excluding specific medication users. Secondly, we used a different CRP cut-off for excluding acute infection (CRP = 10 ml/L). All the analyses were performed using STATA 14.0 (Stata Corporation, College Station, TX, USA).

3. Results

Three main nutrient patterns were identified among 1815 participants. Factor 1 ('vitamin B and folate pattern') was characterised by high intake of total folate, thiamine, riboflavin and niacin; factor 2 ('animal-sourced pattern') was characterised by high intake of animal protein, cobalamin, cholesterol and omega-6; factor 3 ('plant-sourced pattern') had high intake of beta-carotene, vitamin A, lutein, zeaxanthin, vitamin C and fibre (Fig. 2). The three factors explained 62.2% of total variance of nutrients intake.

Sample characteristics according to quartiles of nutrient patterns are presented in Table 1. Demographic, lifestyle, anthropometric and macronutrients as well as energy intake differed across nutrient patterns. Participants with high scores for the vitamin B and folate pattern were more likely to be younger, married or living with a partner and less sedentary. Men in the upper quartiles of the animal-sourced pattern were more likely to be younger, overweight/obese, and current smokers. Participants with intake of the plant-sourced pattern were more likely to be married or living with a partner, higher educated, non-current smoker and non-sedentary. In total, 14.2%, 59% and 32.4% had diabetes, hypertension and low HDL respectively. There were 17.4% and 4.2% of participants taking lipid lowering and diabetes medications.

Median concentrations of CRP and IL-6 across quartiles of each nutrient pattern are shown in Table 2. In the unadjusted model, CRP but not IL-6 level increased significantly across quartiles of the animal-sourced pattern ($p = 0.002$) and decreased significantly across quartiles of the plant-sourced pattern ($p < 0.001$). No differences were found for both CRP and IL-6 levels across quartiles of the vitamin B and folate pattern.

The regression coefficients for the association between quartiles of each nutrient pattern scores and log-transformed inflammatory biomarkers are presented in Table 3. After adjusting for age, demographic, lifestyle factors, waist circumference and chronic disease related markers, compared with the lowest quartile of the animal-sourced pattern, the highest quartile was associated with 20% (exponentiated (0.18) ≈ 1.20) increase of CRP level (p for trend across the quartiles 0.057). Compared with the lowest quartile of the plant-sourced pattern, the highest quartile was associated with 23% (exponentiated (0.21) ≈ 1.23) decrease of CRP (p for trend across the quartiles 0.005). The animal-sourced pattern was positively associated with IL-6 and the plant-sourced pattern was inversely associated with IL-6 after adjusting for age only. There were no associations between the vitamin B and folate pattern and inflammatory biomarkers.

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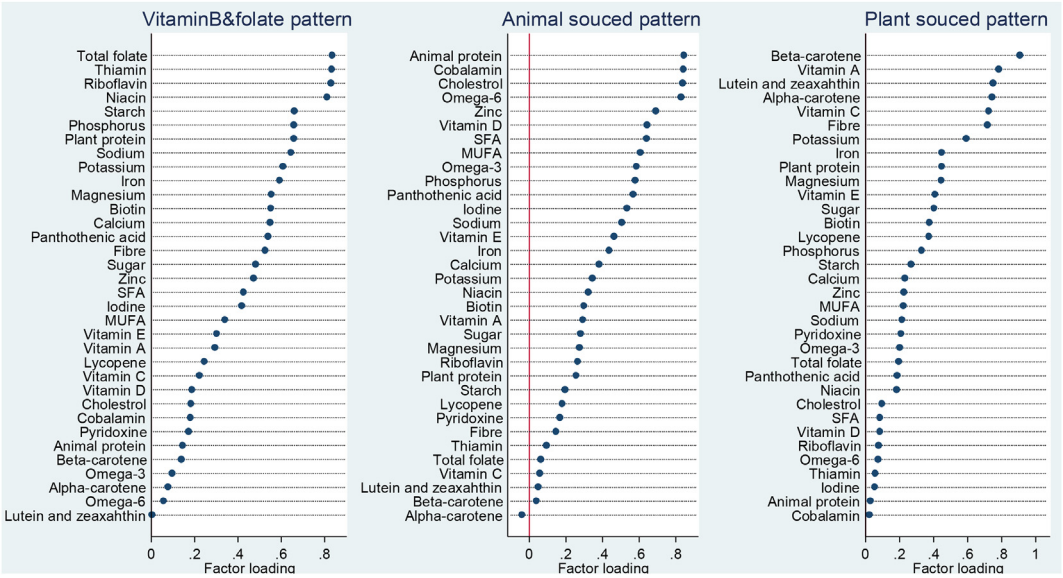

Fig. 2. Factor loadings of nutrient patterns according to factor analysis.

Table 1
Characteristics of participants according to the 1st and 4th quartiles (Q) of the nutrient pattern score for three empirically derived nutrient patterns among MAILES cohort (n = 1815).[a]

	Vitamin B and folate pattern		P-value[b]	Animal-sourced pattern		P-value[b]	Plant-sourced pattern		P-value[b]
	Q1 (n = 454)	Q4 (n = 453)		Q1 (n = 454)	Q4 (n = 453)		Q1 (n = 454)	Q4 (n = 453)	
Age (year), mean (SD)	61.0 ± 11.6	59.0 ± 11.1	0.021	61.0 ± 11.3	58.8 ± 11.3	0.020	59.9 ± 11.8	60.5 ± 10.6	0.15
BMI (kg/m^2), mean (SD)	28.5 ± 4.4	29.0 ± 4.5	0.40	28.5 ± 4.4	29.4 ± 4.7	0.015	28.9 ± 4.6	28.7 ± 4.6	0.69
Waist circumference, mean (SD)	100 ± 12.0	101 ± 12.4	0.80	100 ± 12.6	102 ± 12.7	0.11	101 ± 12.6	101 ± 12.9	0.82
Marriage, n (%)			0.004			0.73			<0.001
Married or living with a partner	330 (75.0)	340 (76.7)		339 (77.4)	342 (76.5)		304 (69.2)	356 (79.8)	
Separated/divorced	58 (13.2)	51 (11.5)		47 (10.7)	62 (13.9)		75 (17.1)	46 (10.3)	
Widowed	32 (7.3)	16 (3.6)		21 (4.8)	18 (4.0)		26 (5.9)	13 (2.9)	
Never married	19 (4.3)	34 (7.7)		29 (6.6)	24 (5.4)		34 (7.7)	27 (6.1)	
Education, n (%)			0.52			0.41			<0.001
≤high school	106 (27.8)	89 (22.4)		87 (22.6)	105 (27.0)		112 (30.7)	91 (22.8)	
Certificate	219 (57.5)	227 (57.0)		221 (57.4)	233 (59.9)		219 (60.0)	223 (55.9)	
Bachelor and above	54 (14.2)	79 (19.8)		74 (19.2)	48 (12.3)		29 (7.9)	82 (20.6)	
Current smoking, n (%)	67 (14.9)	47 (10.4)	0.24	49 (10.8)	83 (18.5)	<0.001	103 (22.8)	38 (8.5)	<0.001
Sedentary lifestyle, n (%)	118 (27.8)	88 (20.5)	0.008	88 (20.7)	104 (23.9)	0.49	126 (29.9)	72 (16.6)	<0.001
Depression, n (%)	46 (10.7)	60 (13.5)	0.27	40 (9.1)	62 (14.2)	0.10	53 (12.2)	47 (10.7)	0.85
Diabetes, n (%)	63 (13.9)	72 (15.9)	0.28	68 (15.0)	70 (15.5)	0.36	65 (14.3)	73 (16.2)	0.49
Apnoea Hypopnoea Index (/h), n (%)			0.61			0.09			0.37
<5	44 (18.2)	40 (15.9)		46 (18.9)	34 (14.3)		46 (19.7)	33 (13.0)	
5–19	119 (49.2)	106 (42.2)		109 (44.9)	102 (43.0)		100 (42.7)	111 (43.9)	
≥20	47 (19.4)	56 (22.3)		52 (21.4)	49 (20.7)		45 (19.2)	59 (23.3)	
Previously diagnosed OSA, n (%)	32 (13.2)	49 (19.5)		36 (14.8)	52 (21.9)		43 (18.4)	50 (19.8)	
Energy intake, mean (SD)	1731 ± 541	2752 ± 668	<0.001	1761 ± 539	2680 ± 676	<0.001	1905 ± 649	2494 ± 649	<0.001
Carbohydrates (% total energy intake)	36.1 ± 6.6	42.1 ± 8.8	<0.001	43.4 ± 8.5	36.1 ± 5.9	<0.001	37.5 ± 6.8	41.3 ± 7.8	<0.001
Protein (% of total energy intake)	19.0 ± 3.7	17.9 ± 2.7	<0.001	17.2 ± 3.1	19.8 ± 3.4	<0.001	18.7 ± 3.6	18.2 ± 2.9	0.13
Fat (% of total energy intake)	41.0 ± 6.7	37.1 ± 5.4	<0.001	35.9 ± 6.8	40.7 ± 5.4	<0.001	40.1 ± 6.4	36.9 ± 5.9	<0.001

[a] Values are means ± SD unless indicated.
[b] P-value was from unadjusted ANOVA analysis of continuous variables and Chi-square for categorical variables.

Sub-group analyses adjusting for age and lifestyle factors (model 2) found that the inverse association between the plant-sourced pattern and CRP was stronger in certain risk factor categories. Among those with AHI ≥20/h or previously diagnosed OSA, high intake of plant -sourced pattern (above median vs below median) had about 42–45% lower CRP level (AHI ≥20/h and diagnosed OSA vs AHI < 19/h, p for interaction 0.213). The association was also stronger in older participants (≥50 years vs <50 years, p for interaction 0.447), and those who were current smokers (p for interaction 0.019) and sedentary behaviours (p for interaction 0.214). However, the inverse association of the plant-sourced pattern with CRP was stronger in those without chronic conditions including diabetes (p for interaction 0.238), normal range of triglycerides level (p for interaction 0.018) and HDL cholesterol level (p for interaction 0.120) (Fig. 3).

When we excluded those statin (n = 76) and metformin (n = 313) users, high intake of plant-sourced pattern showed a beneficial effect (estimates left shifted) on inflammation among those with chronic conditions (diabetes, low high-density lipoprotein), although without statistical significance (Supplemental Fig. 1).

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Table 2
Concentration (median (IQR)) of CRP and IL-6 across quartiles (Q1-Q4) of nutrient patterns.[a]

	Q1	Q2	Q3	Q4	P-value[b]
Vitamin B and Folate pattern					
CRP (ml/L)	1.5 (0.7, 3.2)	1.4 (0.7, 2.8)	1.5 (0.8, 3.0)	1.4 (0.6, 2.8)	0.63
IL-6 (pg/L)	1.6 (1.0, 2.5)	1.5 (1.0, 2.5)	1.5 (1.0, 2.5)	1.5 (0.9, 2.4)	0.67
Animal-sourced pattern					
CRP (ml/L)	1.1 (0.6, 2.7)	1.3 (0.6, 2.7)	1.5 (0.7, 3.0)	1.7 (0.8, 3.4)	0.002
IL-6 (pg/L)	1.4 (1.0, 2.5)	1.5 (0.9, 2.4)	1.6 (1.0, 2.4)	1.6 (1.0, 2.8)	0.18
Plant-sourced pattern					
CRP (ml/L)	1.7 (0.8, 3.5)	1.4 (0.8, 3.0)	1.4 (0.7, 2.9)	1.2 (0.6, 2.4)	<0.001
IL-6 (pg/L)	1.6 (1.1, 2.7)	1.5 (0.9, 2.7)	1.6 (1.0, 2.3)	1.4 (0.9, 2.4)	0.055

[a] Medians of CRP/IL-6 levels with interquartile range (IQR) are presented. CRP and IL-6 were based on 1577 and 1557 observations respectively.
[b] P-value was from unadjusted ANOVA analysis.

Table 3
Regression coefficients for the association between nutrient pattern scores (quartiles) and log-transformed CRP and IL-6.[a]

	N	Q1 (ref)	Q2	Q3	Q4	P for trend[b]
Vitamin B and folate pattern						
log CRP (mg/L)						
Model1	1577		−0.03 (−0.19, 0.13)	−0.02 (−0.17, 0.14)	−0.08 (−0.23, 0.08)	0.356
Model2	1160		−0.02 (−0.21, 0.16)	0.03 (−0.15, 0.21)	−0.04 (−0.22, 0.14)	0.751
Model3	1160		−0.05 (−0.23, 0.12)	−0.00 (−0.18, 0.17)	−0.07 (−0.25, 0.10)	0.514
Model4	1128		−0.05 (−0.23, 0.12)	0.00 (−0.17, 0.18)	−0.04 (−0.22, 0.13)	0.793
log IL-6 (pg/mL)						
Model1	1557		0.02 (−0.09, 0.12)	0.05 (−0.06, 0.16)	−0.00 (−0.11, 0.10)	0.955
Model2	1150		0.02 (−0.11, 0.15)	0.04 (−0.08, 0.17)	0.02 (−0.11, 0.14)	0.788
Model3	1150		0.01 (−0.12, 0.14)	0.03 (−0.10, 0.15)	0.00 (−0.12, 0.13)	0.957
Model4	1118		−0.02 (−0.14, 0.11)	−0.00 (−0.13, 0.12)	−0.01 (−0.14, 0.11)	0.879
Animal-sourced pattern						
log CRP (mg/L)						
Model1	1577		0.04 (−0.12, 0.19)	0.12 (−0.03, 0.28)	0.27 (0.11, 0.42)**	<0.001
Model2	1160		0.09 (−0.09, 0.27)	0.07 (−0.11, 0.26)	0.25 (0.07, 0.44)**	0.011
Model3	1160		0.05 (−0.12, 0.22)	0.08 (−0.10, 0.25)	0.20 (0.02, 0.37)*	0.029
Model4	1128		0.05 (−0.13, 0.22)	0.05 (−0.13, 0.22)	0.18 (0.00, 0.36)*	0.057
log IL-6 (pg/mL)						
Model1	1557		−0.00 (−0.11, 0.11)	0.05 (−0.06, 0.15)	0.11 (0.00, 0.22)*	0.022
Model2	1150		0.01 (−0.12, 0.14)	0.03 (−0.10, 0.15)	0.08 (−0.05, 0.21)	0.218
Model3	1150		−0.01 (−0.13, 0.12)	0.03 (−0.10, 0.15)	0.05 (−0.07, 0.18)	0.342
Model4	1118		0.01 (−0.12, 0.14)	0.04 (−0.08, 0.17)	0.06 (−0.07, 0.19)	0.316
Plant-sourced pattern						
log CRP (mg/L)						
Model1	1577		−0.11 (−0.26, 0.05)	−0.21 (−0.37, −0.06)**	−0.35 (−0.50, −0.19)**	<0.001
Model2	1160		0.02 (−0.16, 0.21)	−0.16 (−0.35, 0.03)	−0.27 (−0.46, −0.09)**	0.001
Model3	1160		0.00 (−0.18, 0.18)	−0.15 (−0.33, 0.04)	−0.24 (−0.42, −0.06)**	0.002
Model4	1128		0.02 (−0.16, 0.19)	−0.12 (−0.30, 0.07)	−0.21 (−0.39, −0.03)*	0.005
log IL-6 (pg/mL)						
Model1	1557		−0.06 (−0.17, 0.04)	−0.08 (−0.19, 0.03)	−0.16 (−0.26, −0.05)**	0.004
Model2	1150		0.00 (−0.13, 0.13)	−0.09 (−0.23, 0.04)	−0.09 (−0.22, 0.04)	0.087
Model3	1150		−0.01 (−0.13, 0.12)	−0.09 (−0.22, 0.04)	−0.08 (−0.21, 0.05)	0.141
Model4	1118		−0.03 (−0.15, 0.10)	−0.05 (−0.18, 0.08)	−0.05 (−0.18, 0.08)	0.417

Model1 adjusted for age.
Model2 further adjusted for education, smoking, stand drinks, physical activity and shift work.
Model3 further adjusted for waist circumference.
Model4 further adjusted for fasting glucose, LDL cholesterol, HDL cholesterol and systolic blood pressure.
*$p < 0.05$. **$p < 0.01$.
[a] All values presented are regression coefficients (95% CI) from linear regression models based on available observations for log CRP (n = 1577) and log IL-6 (n = 1557). Three nutrient patterns were mutually adjusted.
[b] P for trend was calculated using the median value of the factor score by the quartiles of intakes of each pattern.

When we excluded participants with CRP level ≥10 ml/L (approx.5%) instead of 40 ml/L (0.5%), the associations between animal/plant-sourced pattern and inflammation remained (Supplemental Table 1). The interactions between the plant-sourced pattern and OSA was slightly attenuated (Supplemental Fig. 2).

4. Discussion

In this study, we found associations of empirically-derived patterns of nutrient intake and CRP levels. Specifically, a positive association between an animal-sourced pattern and CRP, and an inverse association between plant-sourced pattern and CRP was observed. The inverse association between the plant-sourced pattern and CRP was stronger in participants with higher AHI and previously diagnosed OSA, without diabetes and normal triglycerides and HDL levels, and in current smokers, and those with sedentary behaviours. This may help clinicians manage inflammation from a diet perspective and consider the association with certain risk factors. No independent associations between animal/plant-sourced patterns and IL-6 were found. No associations were observed between vitamin B and folate nutrient pattern and CRP or IL-6.

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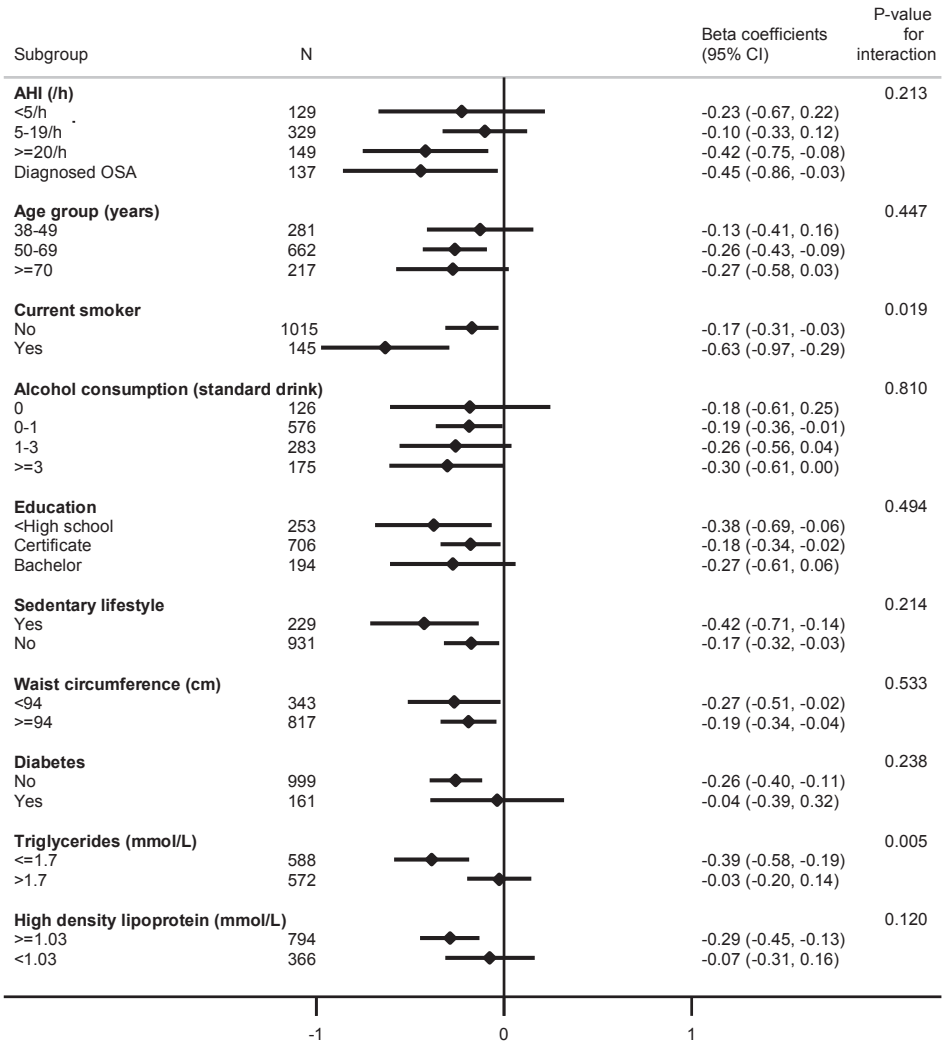

Fig. 3. Subgroup analyses of the associations between plant-sourced pattern (above vs below 50%) and log transformed CRP concentration (excluding CRP > 40 ml/L). Linear regression was conducted adjusting for age, education, smoking, stand drinks, sedentary lifestyle and shift work. P for interaction for AHI (≤19 vs ≥20 and diagnosed OSA) and age group (<50 vs ≥50) was conducted by combining subgroups into dichotomous variable. For diabetes, triglycerides, and high-density lipoprotein, those who had normal range but with medication were treated as positive cases.

4.1. Identification of nutrient patterns

Nutrient patterns identified in our study were in line with the major components of nutrient patterns (eg. animal based, plant based and folate based) that were identified in previous studies [26,27]. For example, a South African study [16] identified animal driven, vitamins and fibre, starch and folate driven, as well as a mixed pattern. Some studies had more specific classifications. In the EPIC study, where 10 European countries were investigated [27], four nutrient patterns were identified although not named. The first two patterns were roughly plant based nutrients and folate and vitamin B. Another two patterns had high intake of vitamin D and polyunsaturated fatty acids and calcium, total protein, and cobalamin, which were integrated as animal-sourced pattern in our study. There were no studies to our knowledge that have examined nutrient patterns and inflammation that we can compare with.

4.2. The association between the animal-sourced pattern and CRP

With multivariable adjustment, the animal-sourced pattern was positively associated with CRP. This is in line with the previous studies on dietary patterns showing that fats and processed meats/western pattern were positively associated with both CRP and IL-6 in women [28] and in both genders [29]. Furthermore, the association was independent of waist circumference and chronic disease related markers. As dietary fats and energy are highly loaded on the animal-sourced pattern, it is possible obesity contributed to alleviated CRP as suggested previously [30]. However, our finding suggests that the association between the animal-sourced pattern and inflammation may not be explained by obesity (particularly abdominal obesity) and chronic diseases related markers including serum glucose level, HDL, and LDL and systolic blood pressure. This is consistent with the MESA study that found the positive association between dietary fats and processed meats pattern and inflammatory markers were independent of waist circumference and CVD risk factors [29].

4.3. The association between the plant-sourced pattern and CRP

The plant-sourced pattern was inversely associated with CRP, which confirms the previous studies that showing anti-inflammatory effects of certain foods and nutrients such as

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vegetables, fruits as well as fibre, monounsaturated and polyunsaturated fatty acids [8]. The stub-study of the PREDIMED also found polyphenol intake was associated with decreased inflammatory biomarkers [31]. It is difficult to fully separate lifestyle habits from diet habits in the multivariable model. It is possible that the cluster of healthy habits such as non-smoking and non-sedentary lifestyles partly contributes to the reduced CRP level. In our study, these healthy habits were more likely to be found in those who had a high intake of the plant-sourced pattern. The inverse association between the plant-sourced pattern and CRP was also independent of waist circumference (model 3) and chronic diseases related markers (model 4). Like the independent association between the animal-sourced pattern and CRP, this also suggests that the inverse association between plant-sourced pattern and CRP may not be caused by obesity or chronic disease related markers.

4.4. The association between animal-sourced pattern/plant-sourced pattern and IL-6

The animal-sourced pattern was positively associated with, and the plant-sourced pattern was inversely associated with IL-6 only when adjusting for age. The associations were attenuated with further adjustments. This is consistent with Nettleton et al. [29] who found the positive/inverse associations of fats and processed meat pattern/vegetable, fish and whole grains pattern with IL-6 (but not CRP) were attenuated with further adjustments. Although it is believed to be induced in the liver by IL-1 and IL-6 as the response to acute infection, CRP has been suggested to be regulated by IL-1 but not IL-6 in healthy subjects [32]. Lack of relationship between IL-6 and CRP has also been suggested in male athletes after exercise [33], suggesting IL-6 may be involved more in metabolic effects than inflammatory responses in certain circumstances. Moreover, IL-6 has shorter plasma half-time [34] and is more susceptible to diurnal variation [35] compared with CRP. These features may affect the concentration and stability of plasma IL-6 and explain why weaker associations were observed with nutrient patterns for IL-6 than CRP.

4.5. Interactions with risk factors

We did not find any interactions between the animal-sourced pattern and lifestyle factors or chronic conditions. However, the inverse association between the plant-sourced pattern and CRP was stronger in participants with higher AHI and diagnosed OSA after adjusting for age, lifestyle factors and waist circumference. Compared with low intake (below the median intake), the higher intake of plant-sourced pattern was associated with more than 40% lower level of CRP. Thus, encouraging a plant based pattern may provide a substantial benefit in terms of reducing inflammation among OSA participants. OSA has been suggested to be associated with elevated levels of CRP and was possibly because of hypoxia and sleep deprivation [36]. In addition, OSA has been regarded as an oxidative stress disorder because the increased free radical production was demonstrated in OSA leukocytes, which may predispose the onset and progression of CVD [37]. Similar stronger associations were also found in smokers, sedentary behavers and older participants. Active smoking has been suggested to increase oxidative stress and reduced blood melatonin levels and impaired respiratory function [38]. Experiments in mice suggested that physical inactivity increases oxidative stress and endothelia dysfunction [39]. In addition, ageing has been suggested to be associated with inflammation and vascular diseases [40].

Taken together, intake of high levels of plant-sourced pattern may provide sufficient fibres and vitamins. Previous studies demonstrated the benefits of fibre and vitamin C in reducing inflammation [41], which could be explained by antioxidant properties of those nutrients. Furthermore, as oxidative status may be highlighted in those with higher AHI, who smoke and who lack physical activity, the body may better respond to antioxidants nutrients (eg. vitamin C and fibre).

The inverse association between the plant-sourced pattern and CRP was stronger among those who did not have diabetes or had normal level of triglycerides and HDL. It is possible that those who had these chronic conditions are already under treatment, and the medication may overshadow any beneficial effect of diet. A German randomized controlled trial demonstrated no effect of the Mediterranean diet on inflammation in patients with coronary artery disease, which may be mainly due to the use of statins medication [12]. Metformin has been suggested to restore antioxidant status and inflammation in type 2 diabetes patients [42]. In our study, when we excluded those statin/metformin users, a high intake of plant-sourced pattern showed a trend of beneficial effect on inflammation among those with diabetes and low HDL, although without statistical significance. However, a high proportion of those with diabetes were undiagnosed and without treatment. This may explain the attenuated benefits from plant-sourced pattern in this group. It is noted that the interaction between the plant-sourced pattern and OSA became not statistically significant when excluding CRP $\geq$ 10 ml/L ($10 < CRP < 40$, $n = 63$, $CRP \geq 40$, $n = 9$). Among those, 21 out of 23 (those underwent PSG) had AHI $\geq$4. Excluding these participants would result in a reduced sample power.

4.6. Vitamin B and folate pattern and inflammation

We did not find any associations between the vitamin B and folate pattern and inflammation. The South African study mentioned previously [16] for the first time reported the positive association between a starch and folate nutrient pattern and BMI in adolescents. However, there are no associations after full adjustment. In that study, they did not assess nutrients pattern and inflammation.

Although we have detailed information on lifestyle, chronic disease and biomarker measurements in a relative large cohort as the major strength of this study, several limitations that must be considered. Firstly, the dietary intake was estimated according to the self-reported FFQ rather than weighed 24-h food records, which are difficult and impractical to obtain in studies with large sample sizes. Secondly, the nutrient groups were subjectively summarised and generated empirically. However, nutrient patterns based on nutrient groups were similar with previous studies. Thirdly, no cause-effect relations in the general population and in females can be inferred as the analysis was cross-sectional and limited to males. In addition, asynchronous data collection for diet and biomarker and the conduct of PSG should be noted.

This study confirms the potential role of diet in inflammation regulation from the nutrient patterns perspective. As inflammation is involved in the pathological development of a range of chronic diseases, our study has clinical and public health implications. In conclusion, our findings suggest that an animal-sourced pattern was associated with elevated CRP level, while a plant-sourced pattern was associated with reduced CRP level in middle-aged and elderly men. The benefits from a plant-sourced pattern may be stronger in subgroups with high AHI, current smokers and those with sedentary lifestyles. Further longitudinal studies are needed to confirm these findings.

Conflict of interest

The authors declared that there are no conflicts of interest.

Please cite this article in press as: Cao Y, et al., Nutrient patterns and chronic inflammation in a cohort of community dwelling middle-aged men, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.06.018

Acknowledgements

The present study was supported by the National Health and Medical Research Council of Australia (NHMRC Project Grant 627227). The authors' contributions are as following: Y.C carried out the data analyses and wrote the manuscript; Z.S and G.W contributed to conceiving the study design, reviewing the data analyses; G.W, Z.S, R.A, S.A and AWT critically reviewed the manuscript and approved the final version.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2016.06.018.

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6.2 Errata for the paper:

In 2.6.2 data analysis, ‘linear regression analyses were used to test the association between nutrient pattern scores (continuous variable) and CRP and IL-6’. ‘Continuous variable’ should be corrected to ‘categorical variable’.

6.3 Supplemental results of nutrient patterns and sleep outcomes

In the study presented above, I did not include the associations between nutrient patterns and sleep outcomes in the analysis. The reasons are as follows: 1) the associations between dietary patterns and sleep outcomes have been explored in the second research of this thesis. Although known advantages of nutrient pattern analysis has been explained, both of dietary pattern and nutrient pattern analyses addressed the whole diet rather than single foods/nutrients intake; 2) a large body of evidence suggests that dietary factors have anti/pro-inflammatory effects, and sleep disorders are also closely linked with inflammation. It is important to investigate the interactions among dietary factors, inflammation and sleep disorders as well as lifestyle factors and other chronic conditions together in our study population with the pro-inflammatory profile; 3) many studies have examined the associations between dietary patterns and inflammation, however, no studies have examined the association between nutrient patterns and inflammation.

Although not included in the publication, I did check the associations between nutrient patterns and sleep outcomes (the same outcomes with study two, i.e. sleep onset, PSG measured total sleep time, OSA, and self-reported sleepiness and poor sleep quality). The results are presented below. In brief, the results of the associations between nutrient patterns and sleep outcomes are generally similar with the results of the associations using dietary patterns. The plant-sourced nutrient pattern/the prudent dietary pattern was inversely associated with SOL and the animal-sourced nutrient pattern/the western dietary pattern was positively associated with AHI, although with different magnitude. For the plant-sourced pattern, compared with the lowest quartile of the plant-sourced pattern, the highest quartile was associated with a reduced SOL (relative risk ratio (RRR) 0.46, 95% CI 0.22 - 0.96) but with no significant trend across the quartiles (Appendix A. Supplemental Table 6.1).

Comparing with the lowest quartile of the animal-sourced pattern, the highest quartile was associated with increased AHI (RRR 1.57, 95% CI 0.81 - 3.02), but with a significant increased trend of AHI across the quartiles (p for trend 0.028) (Appendix B. Supplemental Table 6.2).

There were no associations between the quartiles of nutrient patterns and TST, self-reported daytime sleepiness and poor sleep quality (Appendix C and D. Supplemental Table 6.3 and 6.4).

CHAPTER 7 DISCUSSION, FUTURE DIRECTIONS AND CONCLUSION

7.1 Summary of findings

This thesis addresses the emerging public health concern of sleep disorders, and demonstrates the potential associations between dietary factors and sleep outcomes at the population level. The findings revealed that a general healthy diet, such as a prudent pattern diet, which is characterized by vegetables, fruits and legumes, has benefits in facilitating sleep onset. On the other hand, a high fat intake or western pattern diet, which is characterized by processed meat and takeaway foods, increases the risk of OSA and daytime sleepiness. The main findings between dietary factors and sleep outcomes in this thesis are summarised in Table 7.1.

Table 7. 1 Findings summary of the associations between dietary factors and sleep outcomes in this thesis

Dietary factors	Sleep outcomes				
	AHI	SOL	TST	Daytime sleepiness	Poor sleep quality
Carbohydrate	Null	Null	Null	Null	Null
Protein	Null	Null	Null	Null	Null
Fat	+	Null	Null	+	Null
Prudent dietary pattern	Null	-	Null	Null	Null
Western dietary pattern	+	Null	Null	Null	Null
Plant-sourced pattern	Null	-	Null	Null	Null
Animal-sourced pattern	+	Null	Null	Null	Null
Vitamin B and folate pattern	Null	Null	Null	Null	Null

'+' indicates a positive association between the dietary factor and sleep outcomes, - indicates a negative association between the dietary factor and sleep outcomes. Detailed values please refer to Table 4 in Chapter 4, Table 5.4 in Chapter 5, Supplemental Table 5.3 in Chapter 5, Appendix A. Supplemental Table 6.1 and Appendix B. Supplemental Table 6.2 in the Appendixes.

A range of factors including demographic, lifestyle and chronic conditions were considered when assessing the associations between dietary factors and sleep outcomes in this thesis. Figure 7.1 shows the associations between diets and CRP and the clustering by demographic and lifestyle factors in this thesis. A healthy diet was inversely associated with CRP and an unhealthy diet was positively associated with CRP. In addition, an unhealthy diet, particularly a diet with high fat intake, was associated with increased AHI, which may be via increased body mass index (BMI). No associations were found between a healthy diet and AHI.

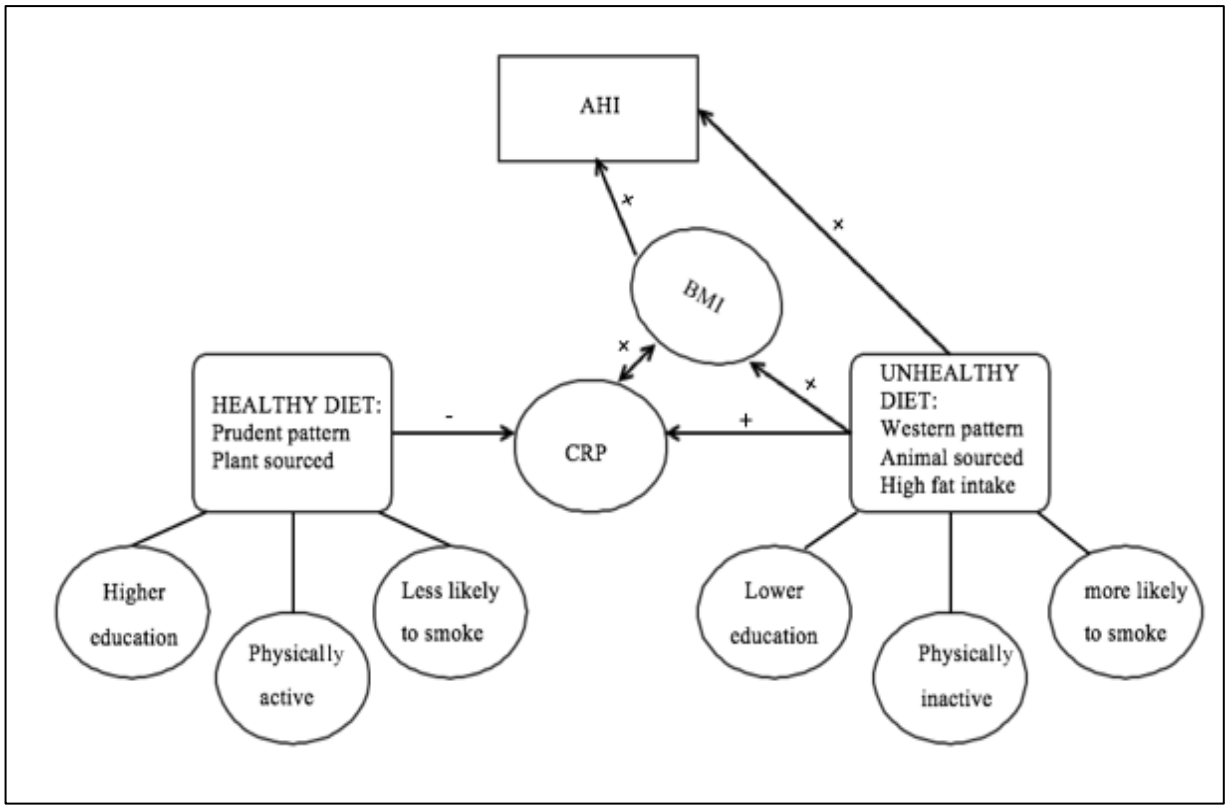

Figure 7. 1 Associations among dietary factors, inflammation, lifestyle factors and sleep outcomes among Australian men

'+' indicates a positive association and '-' indicates an inverse association

AHI, apnoea-hypopnea index. BMI, body mass index. CRP, C-reactive protein.

7.2 Potential explanations for the link between diet and sleep

7.2.1 BMI as a mediator

Previous studies have suggested obesity may be the most important risk factor for sleep apnoea [172]. High fat intake was found to be associated with increased AHI in this thesis, which may be possibly explained by excessive body weight. Therefore, mediation effects (i.e. explain the pathway between high fat diet and AHI) were examined.

As demonstrated in the Supplemental Table 3 and Figure 1 of the first study included in Chapter 4, the effect of BMI on AHI was five times stronger than the effect from fat intake, and 30% of the total effect of fat intake on AHI came from the contribution of BMI. This indicates that BMI mediates the association between fat intake and AHI. Interestingly, the association between high fat intake and increased AHI was more prominent in those who had BMI below 25 kg/m^2. It is possible that the effect of a high fat diet on those already overweight or obese is relatively weaker than those with normal weight in terms of increase in BMI.

In Australia, 62.8% of adults were estimated to be overweight (35.3%) or obese (27.5%) in 2012 according to Australian Bureau of Statistics [173]. Great importance in Australia is placed on addressing the overweight/obese population, with a major role in reducing high fat diets. There is also potential to prevent OSA via weight management through dietary interventions. This may also be true in other developed countries.

Similarly, the western dietary pattern and the animal-sourced nutrient pattern are positively associated with fat, and similarly increase AHI via BMI found in this thesis. However, the effect was not as strong as single high fat intake.

As shown in Figure 7.1 an unhealthy diet increases AHI but this does not necessarily mean a heathy diet would decrease AHI. A healthy diet is still encouraged as a result of its inverse association with CRP and positive association with other healthy lifestyle factors.

7.2.2 Clustering of lifestyle factors

The inverse association between the prudent dietary pattern and SOL as shown in Chapter 5 may be explained by glycaemic index, as suggested in experimental studies [25]. However, unlike the direct effect that a meal has on sleep, which was tested in the previous studies, habitual dietary patterns and their relationship with sleep outcomes was examined in this thesis. Dietary patterns may be also closely linked with many lifestyle factors. For example, a western dietary pattern may be associated with late bedtime due to social functions; while a prudent dietary pattern may be accompanied by a prudent lifestyle and simple social activities especially before bed. In addition, excessive stress may also affect sleep adversely. A healthy dietary pattern has been found to reduce depression which was probably due to the anti-inflammatory properties [163-165].

Moreover, different diets are associated with lifestyle factors including smoking and physical activity. In the second research (Chapter 5), dietary patterns and sleep outcomes were investigated. It showed the prevalence of smoking was lower among those who had a prudent dietary pattern rather than those who consumed a western dietary pattern (6% vs 25%). Those who had the prudent pattern diet were more likely to be physically active (88%) than those who had the western pattern (67%) after adjusting for age. Similarly, as shown in study 3 (Chapter 6) when comparing with the lowest quartile of the plant-sourced pattern, participants who had the highest quartile were less likely to be a smoker or undertake sedentary behaviour (9% vs 23%, and 17% vs 30% respectively); comparing with the lowest quartile of the animal-sourced pattern, participants who had the highest quartile were more

likely to smoke and be sedentary (18.5% vs 10.8% and 23.9% vs 20.7% respectively). The findings in this thesis are supported by other studies. A large Spanish cross-sectional study (n=3847) assessed the association between demographic and life styles and dietary patterns in adults. Results showed that young, sedentary, single males were more likely to follow a 'Western' dietary pattern rather than a ‘Mediterranean diet’ [174]. In the Singapore Chinese Health study, it was found that those who had a ‘Vegetable-Fruits-Soy’ pattern were less likely to smoke compared those who consumed a ‘Dim-sum-and meat rich’ pattern [36].

These findings highlight the potential clustered lifestyle behaviours associated with healthy and unhealthy diets. The effects of diet on health may in fact reflect the overall effects of the clustering of diet and lifestyle.

7.2.3 Link with inflammation

Research on the influence of nutrition on inflammation has revealed generally two types of foods/diets: pro-inflammatory and anti-inflammatory [44]. This indicates the crucial role of dietary factors in chronic inflammation and disease progress. Similarly, the findings in this thesis suggest two groups of foods/nutrients: a high fat intake/western pattern/animal-sourced pattern and a prudent pattern/plant-sourced pattern. These two groups of foods/nutrients are associated differently with inflammation. The study included in Chapter 6 suggested a positive association between the animal-sourced pattern and CRP, and the association is independent of obesity and chronic diseases related markers including HDL and LDL. On the other hand, the plant-sourced pattern was inversely associated with CRP, and the association seemed to be more prominent in those with severe OSA. OSA has been regarded as an oxidative stress disorder [175], and nutrients in the plant-sourced pattern such as fibre and vitamin C have strong anti-oxidant effects and reduce inflammation [176], which may be one of the explanations. As inflammation is involved in the pathological

development of a range of chronic diseases, highlighting the importance of considering other risk factors such as OSA in inflammation management is crucial.

7.3 Implications/significance

This thesis has clinical and public health implications. For clinicians, as dietary factors and sleep closely interacted with metabolic functioning, inflammation and chronic diseases, a focus on management of the pre-inflammatory profile, particularly in weight loss, may facilitate sleep in people with OSA. From the public health point of view, it urges increased demand for developing and implementing nutritional strategies to improve diet quality in the population, which could lead to lower health care costs.

7.4 Limitations

Although the limitations have already been discussed separately in the studies in Chapter 4-6, a brief summary and additional of limitations of the thesis are presented as below.

In all studies presented in this thesis, cross-sectional analyses have been conducted which leaves the causal effect to be confirmed. Dietary intake data were collected approximately about 2.5 years prior to the sleep study data, which allows the possibility of those with sleep problems changing their dietary habits before the sleep study was performed. As about 19% of the loss to follow-up between MAILES 1 and MAILES 2 were due to death, it can be speculated that those subjects may have poor diet and sleep. Thus, the association between diet and sleep may be underestimated. Dietary intake was assessed using FFQ, which may have several concerns: 1) arbitrary grouping of the food items may not correspond to the perception of the respondent; 2) it may not reflect meal specific food intake information such as 24-hour food record or actual weighing; 3) it does not measure portion sizes and energy intake cannot be estimated; and 4) depends on eating habits and population; 5) less

sensitive to measures of absolute intake for specific nutrients. However, FFQ has been validated by Cancer Council Victoria and it is impractical to conduct 24-hour food recall or actual weighing in studies with large sample sizes, and 24-hour food recall does not capture the long-term dietary habits as FFQ does. Furthermore, dietary under-reporters were not excluded, which may potentially affect the results. However, the number of under-reporters is small in the study population [177]. It is also noted that the NUTTAB95 database was used for foods/nutrients calculation, which may not provide update food composition information. However, this calculation was performed by Cancer Council Victoria.

For factor analysis, the subjective nature of the PCA method to extract dietary patterns should be acknowledged. The subjective food grouping should also be acknowledged although the reference we used suggested 40 groups [157]. 'Unsaturated and saturated spread' were combined into one group 'spread', and another two groups 'other bread' and 'dressing' were added, resulting in a total of 41 groups. It is also noted that other methods such as cluster analysis and reduced rank regression (RRR) are available for extracting dietary patterns. Cluster analysis identifies dietary exposure categories with homogenous groups, and clusters are mutually exclusive and continuous, making it easier to handle compared with PCA. But cluster analysis is easily affected by outliers which PCA is not [37]. Despite clear difference, evidence has suggested that eating patterns are revealed by either method. On the other hand, RRR explains as much as possible variation in the responsible variable (outcome related variable). RRR seems to be a promising method to determine which dietary patterns are associated with development of diseases. However, the usefulness of RRR needs further confirmation in future studies for choosing other disease-related response variables [178]. In constructing dietary patterns, factor loading above 0.3 is often used as the cut-off due to the complex nature of diet. In the thesis although a cut-off was not selected, the interpretation and naming of dietary patterns follows the cut-

off of 0.3. As dietary patterns may also be subject to different group of people, those who had prudent dietary pattern may also have western dietary pattern, at different degrees. Thus we grouped the subjects into three groups according to the degree of the consumption of two dietary patterns/factors (prudent and western): prudent, western and mixed. The difference between the two patterns/factors was decided as two quartiles. If subjects whose consumption of the prudent pattern was at the first quartile, and the consumption of the western was at the third quartile or higher, then these subjects were allocated to the western pattern. Vice versa for the prudent pattern (Appendix E). Similarly, this subjective nature of allocation should also be acknowledged. Timing of food intake plays a role in circadian rhythm [179], however this was not able to be assessed in this thesis. In addition, the study population was limited to men, so the conclusions may not apply for women.

7.5 Future directions

7.5.1 Prospective studies

Prospective studies are required to evaluate the effect of dietary factors on sleep outcomes in relation to lifestyle factors and chronic inflammation. This may lead to an improved understanding of factors associated with dietary factors, and ultimately to improved outcomes. The causal relationship between dietary factors and sleep outcomes may be more clearly revealed.

7.5.2 Large scale dietary interventions

If prospective studies further confirm the associations between dietary factors and sleep outcomes, dietary interventions may be encouraged among people with sleep disorders. Dietary interventions may result in lower levels of psychosocial stress and provide long-

term outcomes for the treatment and prevention of sleep problems and be seen as an alternative to medication use.

7.5.3 Timing of food intake

Human bodies have a built-in circadian rhythm (approximately 24 hours) in behaviour and physiology, in response to the daily light/dark cycle. The circadian system readies the organisms to feed and fast at different times; likewise, feeding can also modify the circadian rhythm at both the molecular and behavioural levels [180, 181]. Peripheral tissue clocks such as the liver clock are particular sensitive to the composition and timing of food consumed. The compositions of foods have been shown to affect circadian rhythms in rodents and humans. In mice, high-fat diet blunted diurnal rhythmicity of gut microbiota structure and function [182]. Switching from a high-carbohydrate (55%) low-fat (30%) diet to an isoenergetic low-carbohydrate (40%) high-fat (45%) diet delayed and increased the amplitude of cortisol rhythms and altered PER gene expression rhythms in monocytes [183]. Timing of food consumed has also shown differences in both metabolic dysregulations and sleep regulation in mice and humans. Mice fed with normal chow diet at the rest phrase gained more weight than those fed at the active phrase, suggesting asynchrony between metabolically active organs [184]. A high-fat diet at dinner was associated with persistent short sleep, but a high-fat breakfast prevented daytime falling asleep in a longitudinal study of Chinese adults [185].

Interactions between the inner body biological clock and food intake need to be addressed in future research. Nutritional epidemiological studies that incorporate sleep outcomes are needed. As mentioned in the limitation it is impractical to use 24-hour food recall that includes information on the timing of meals in studies with large sample sizes. Additional

meal occasion (breakfast, lunch or dinner) options provided in the questionnaires may be an alternative for large-scale studies.

7.5.4 Types of fat

The types of fat consumed may play a different role in sleep regulation, although most focus has been on the effect on cardiovascular and metabolic functions. Dietary saturated fat has been shown to harm the cardiovascular system, however a recent meta-analysis provided controversial evidence, which concluded that there is not yet enough evidence to support cardiovascular guidelines encouraging low consumption of total saturated fatty acids [186]. The meta-analysis did not compare saturated fat with other nutrients, limiting the review to draw such conclusions. Adela Hruby *et. al.* [187] supported the link between high saturated fat intake and cardiovascular disease risks, and emphasized that replacing saturated fat with unsaturated fat and polyunsaturated fat might reduce the risk of cardiovascular diseases. Trans fat, on the contrary, has consistently shown a harmful effects on human health including coronary heart disease, brain and nervous dysfunction as well as depression [188]. Certain fat types may affect sleep quality. St-Onge's group found a high saturated fat was associated with less restorative sleep with more arousals [28].

All these findings emphasize the potential role of different types of fat in health outcomes including sleep regulation, which may highlight further future research. This may lead to a better understanding of the effect of fat on sleep outcomes, and avoid excess criticism of fat intake.

7.5.5 Validation in other populations

As diet and lifestyle factors differ by countries, our findings need to be validated in other populations, as well as in women and different age groups. As nutrition and sleep

requirements change by age, the association in younger adults may differ from that in older adults. Exploring the association in other age groups will provide a comprehensive understanding of the association.

7.5.6 Establishment of cohort with healthy subjects

Additionally, as the study subjects in this thesis are pre-inflammatory, establishing a cohort of healthy subjects may help elucidate the physiological pathway between dietary exposures and the risk of sleep disorders.

7.6 Conclusion

This work has demonstrated the associations between dietary factors and sleep outcomes (both objective and subjective measures) at the population level in men, contributing to the lack of such evidence in the literature. Overall, it appears that dietary fat intake exacerbates the severity of OSA, and is mainly due to excessive body weight. High dietary fat intake was positively associated with daytime sleepiness. A prudent dietary pattern that is rich in fresh fruit, vegetable and whole grain may facilitate faster sleep onset. A plant-sourced nutrients pattern that is rich in beta-carotene, vitamin A, lutein and zeaxanthin is encouraged for inflammation management. Importantly, subjects, particularly those with severe OSA and sedentary behaviours, may benefit in reducing inflammation from eating plant-sourced diets. Clinical and public health implications are indicated to address lifestyle behaviours when providing dietary interventions for better health outcomes.

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APPENDIXES

Appendix A. Supplemental Table 5.4 from study in Chapter 5

Supplemental Table 1 Allocation of subjects into three groups according to different consumptions of quartiles of two dietary patterns/factors

Difference of quartiles of prudent and western factors (from factor analysis)	Dietary patterns
3	Prudent
2	Prudent
1	Mixed
0	Mixed
-1	Mixed
-2	Western
-3	Western

Appendix B. Supplemental Table 6.1 from study in Chapter 6

Supplemental Table 1. Associations (relative risk ratio (RRR) 95%CI) between quartiles of the nutrient patterns and SOL

		Quartiles of nutrient patterns					n
		Q1 (ref)	Q2	Q3	Q4	P for trend[1]	
SOL (min)				**Vitamin B and Folate**			
<7 (ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	184
7-30	Model 1 [2]	1.00	1.33 (0.82 - 2.18)	1.16 (0.71 - 1.91)	0.94 (0.58 - 1.52)	0.46	456
≥30	Model 1 [2]	1.00	0.99 (0.51 - 1.91)	1.77 (0.95 - 3.27)	1.17 (0.63 - 2.19)	0.66	144
							Subtotal: 784
<7 (ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	150
7-30	Model 2 [3]	1.00	1.12 (0.64 - 1.95)	1.19 (0.67 - 2.09)	0.85 (0.49 - 1.48)	0.37	383
≥30	Model 2 [3]	1.00	0.84 (0.39 - 1.81)	1.82 (0.90 - 3.69)	1.05 (0.51 - 2.14)	0.86	119
							Subtotal: 652
<7 (ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	150
7-30	Model 3 [4]	1.00	1.09 (0.63 - 1.91)	1.17 (0.66 - 2.06)	0.83 (0.48 - 1.45)	0.34	383
≥30	Model 3 [4]	1.00	0.85 (0.39 - 1.82)	1.82 (0.90 - 3.70)	1.04 (0.51 - 2.14)	0.86	119
							Subtotal: 652
<7 (ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	144
7-30	Model 4 [5]	1.00	0.96 (0.54 - 1.70)	1.17 (0.65 - 2.11)	0.74 (0.42 - 1.31)	0.22	375
≥30	Model 4 [5]	1.00	0.73 (0.33 - 1.59)	1.88 (0.91 - 3.91)	0.94 (0.45 - 1.96)	0.99	116
							Subtotal: 635
SOL (min)				**Animal-sourced pattern**			

<7 (ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	184
7-30	Model 1 [2]	1.00	1.22 (0.74 - 1.99)	1.45 (0.87 - 2.40)	0.99 (0.62 - 1.60)	0.99	456
≥30	Model 1 [2]	1.00	1.17 (0.63 - 2.17)	1.18 (0.63 - 2.23)	0.75 (0.41 - 1.40)	0.31	144
							Subtotal: 784
<7 (ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	150
7-30	Model 2 [3]	1.00	1.32 (0.76 - 2.30)	1.63 (0.93 - 2.88)	1.10 (0.64 - 1.88)	0.73	383
≥30	Model 2 [3]	1.00	1.23 (0.61 - 2.48)	1.30 (0.63 - 2.68)	0.82 (0.40 - 1.68)	0.38	119
							Subtotal: 652
<7 (ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	150
7-30	Model 3 [4]	1.00	1.31 (0.75 - 2.28)	1.63 (0.92 - 2.86)	1.08 (0.63 - 1.85)	0.78	383
≥30	Model 3 [4]	1.00	1.23 (0.61 - 2.48)	1.30 (0.63 - 2.68)	0.82 (0.40 - 1.68)	0.38	119
							Subtotal: 652
<7 (ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	144
7-30	Model 4 [5]	1.00	1.39 (0.78 - 2.46)	1.68 (0.94 - 3.00)	1.08 (0.62 - 1.89)	0.84	375
≥30	Model 4 [5]	1.00	1.30 (0.63 - 2.67)	1.30 (0.62 - 2.73)	0.85 (0.41 - 1.77)	0.37	116
							Subtotal: 596
SOL (min)				**Plant-sourced pattern**			
<7 (ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	184
7-30	Model 1 [2]	1.00	0.94 (0.57 - 1.54)	1.18 (0.71 - 1.98)	0.75 (0.46 - 1.23)	0.33	456
≥30	Model 1 [2]	1.00	0.46 (0.25 - 0.88)*	0.76 (0.40 - 1.43)	0.56 (0.30 - 1.02)	0.18	144
							Subtotal: 784
<7 (ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	150
7-30	Model 2 [3]	1.00	0.81 (0.46 - 1.44)	1.10 (0.60 - 2.03)	0.72 (0.40 - 1.29)	0.37	383
≥30	Model 2 [3]	1.00	0.35 (0.17 - 0.74)**	0.61 (0.29 - 1.30)	0.51 (0.25 - 1.03)	0.19	119

							Subtotal: 652
<7 (ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	150
7-30	Model 3 [4]	1.00	0.81 (0.46 - 1.43)	1.12 (0.61 - 2.06)	0.73 (0.41 - 1.31)	0.40	383
≥30	Model 3 [4]	1.00	0.35 (0.17 - 0.74)**	0.61 (0.29 - 1.29)	0.51 (0.25 - 1.03)	0.19	119
							Subtotal: 652
<7 (ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	144
7-30	Model 4 [5]	1.00	0.79 (0.44 - 1.43)	1.15 (0.61 - 2.17)	0.72 (0.39 - 1.30)	0.39	375
≥30	Model 4 [5]	1.00	0.32 (0.15 - 0.68)**	0.63 (0.29 - 1.37)	0.46 (0.22 - 0.96)*	0.16	116
							Subtotal: 635

[1] P for trend was calculated using the median value of the factor score by the quartiles of intakes of each pattern
[2] Model1 adjusted for age.
[3] Model2 further adjusted for education, smoking, stand drinks, physical activity and shift work.
[4] Model3 further adjusted for waist circumference.
[5] Model4 further adjusted for fasting glucose, LDL cholesterol, HDL cholesterol and systolic blood pressure.
SOL, sleep onset latency
*p<0.05. **p<0.01

Appendix C. Supplemental Table 6.2 from study in Chapter 6

Supplemental Table 2 Associations (relative risk ratio (RRR) 95%CI) between quartiles of the nutrient patterns and AHI

		Quartiles of nutrient patterns					n
		Q1 (ref)	Q2	Q3	Q4	P for trend[1]	
AHI (/h)				**Vitamin B and Folate**			
<5 (ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	169
5-19	Model 1 [2]	1.00	1.23 (0.75 - 2.01)	1.63 (0.98 - 2.71)	0.86 (0.53 - 1.39)	0.81	421
≥20	Model 1 [2]	1.00	1.00 (0.57 - 1.75)	1.13 (0.63 - 2.01)	0.64 (0.37 - 1.13)	0.33	194
							Subtotal: 784
<5 (ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	139
5-19	Model 2 [3]	1.00	0.98 (0.56 - 1.73)	1.33 (0.75 - 2.35)	0.73 (0.42 - 1.28)	0.90	353
≥20	Model 2 [3]	1.00	0.78 (0.41 - 1.48)	0.83 (0.43 - 1.60)	0.53 (0.28 - 1.01)	0.22	160
							Subtotal: 652
<5 (ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	139
5-19	Model 3 [4]	1.00	1.00 (0.57 - 1.75)	1.34 (0.76 - 2.38)	0.74 (0.43 - 1.29)	0.91	353
≥20	Model 3 [4]	1.00	0.79 (0.41 - 1.51)	0.84 (0.43 - 1.62)	0.54 (0.28 - 1.03)	0.39	160
							Subtotal: 652
<5 (ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	137
5-19	Model 4 [5]	1.00	1.06 (0.60 - 1.90)	1.34 (0.75 - 2.39)	0.79 (0.45 - 1.40)	0.72	343
≥20	Model 4 [5]	1.00	0.86 (0.44 - 1.66)	0.84 (0.43 - 1.64)	0.59 (0.30 - 1.14)	0.51	155
							Subtotal: 635
				Animal-sourced pattern			

<5 (ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	169
5-19	Model 1 [2]	1.00	1.48 (0.90 - 2.43)	1.14 (0.70 - 1.86)	1.09 (0.67 - 1.77)	0.23	421
≥20	Model 1 [2]	1.00	1.15 (0.65 - 2.05)	0.96 (0.54 - 1.68)	1.05 (0.60 - 1.84)	0.06	194
							Subtotal: 784
<5 (ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	139
5-19	Model 2 [3]	1.00	1.35 (0.78 - 2.36)	1.24 (0.72 - 2.14)	1.21 (0.69 - 2.11)	0.14	353
≥20	Model 2 [3]	1.00	1.27 (0.66 - 2.46)	1.16 (0.61 - 2.21)	1.60 (0.84 - 3.03)	0.026	160
							Subtotal: 652
<5 (ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	139
5-19	Model 3 [4]	1.00	1.35 (0.78 - 2.36)	1.24 (0.72 - 2.14)	1.22 (0.70 - 2.12)	0.19	353
≥20	Model 3 [4]	1.00	1.27 (0.66 - 2.46)	1.16 (0.61 - 2.21)	1.61 (0.85 - 3.07)	0.040	160
							Subtotal: 652
<5 (ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	137
5-19	Model 4 [5]	1.00	1.22 (0.69 - 2.15)	1.22 (0.69 - 2.13)	1.17 (0.66 - 2.07)	0.15	343
≥20	Model 4 [5]	1.00	1.18 (0.60 - 2.29)	1.15 (0.59 - 2.23)	1.57 (0.81 - 3.02)	0.028	155
							Subtotal: 596
				Plant-sourced pattern			
<5 (ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	169
5-19	Model 1 [2]	1.00	1.19 (0.72 - 1.95)	0.89 (0.54 - 1.46)	1.01 (0.63 - 1.63)	0.17	421
≥20	Model 1 [2]	1.00	1.52 (0.85 - 2.72)	1.67 (0.95 - 2.94)	1.05 (0.59 - 1.90)	0.07	194
							Subtotal: 784
<5 (ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	139
5-19	Model 2 [3]	1.00	0.96 (0.55 - 1.70)	0.70 (0.39 - 1.24)	0.84 (0.48 - 1.47)	0.88	353
≥20	Model 2 [3]	1.00	1.29 (0.66 - 2.54)	1.09 (0.56 - 2.13)	0.88 (0.45 - 1.75)	0.34	160

							Subtotal: 652
<5 (ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	139
5-19	Model 3 [4]	1.00	0.97 (0.55 - 1.71)	0.69 (0.39 - 1.23)	0.84 (0.48 - 1.47)	0.79	353
≥20	Model 3 [4]	1.00	1.30 (0.66 - 2.56)	1.08 (0.55 - 2.12)	0.88 (0.45 - 1.75)	0.16	160
							Subtotal: 652
<5 (ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	137
5-19	Model 4 [5]	1.00	1.03 (0.58 - 1.83)	0.76 (0.42 - 1.37)	0.92 (0.52 - 1.62)	0.87	343
≥20	Model 4 [5]	1.00	1.37 (0.69 - 2.71)	1.18 (0.59 - 2.35)	0.94 (0.47 - 1.89)	0.18	155
							Subtotal: 635

[1] P for trend was calculated using the median value of the factor score by the quartiles of intakes of each pattern

[2] Model1 adjusted for age.

[3] Model2 further adjusted for education, smoking, stand drinks, physical activity and shift work.

[4] Model3 further adjusted for waist circumference.

[5] Model4 further adjusted for fasting glucose, LDL cholesterol, HDL cholesterol and systolic blood pressure.

AHI, apnoea-hypopnea index.

Appendix D. Supplemental Table 6.3 from study in Chapter 6

Supplemental Table 3 Associations (relative risk ratio (RRR) 95%CI) between quartiles of the nutrient patterns and TST

		Quartiles of nutrient patterns					n
		Q1 (ref)	Q2	Q3	Q4	P for trend[1]	
TST (min)				**Vitamin B and Folate**			
337-412(ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	197
<337	Model 1 [2]	1.00	1.23 (0.75 - 2.01)	1.63 (0.98 - 2.71)	0.86 (0.53 - 1.39)	0.42	391
≥412	Model 1 [2]	1.00	1.00 (0.57 - 1.75)	1.13 (0.63 - 2.01)	0.64 (0.37 - 1.13)	0.10	196
							Subtotal: 784
337-412(ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	164
<337	Model 2 [3]	1.00	0.98 (0.56 - 1.73)	1.33 (0.75 - 2.35)	0.73 (0.42 - 1.28)	0.27	329
≥412	Model 2 [3]	1.00	0.78 (0.41 - 1.48)	0.83 (0.43 - 1.60)	0.53 (0.28 - 1.01)	0.06	159
							Subtotal: 652
337-412(ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	164
<337	Model 3 [4]	1.00	1.00 (0.57 - 1.75)	1.34 (0.76 - 2.38)	0.74 (0.43 - 1.29)	0.28	329
≥412	Model 3 [4]	1.00	0.79 (0.41 - 1.51)	0.84 (0.43 - 1.62)	0.54 (0.28 - 1.03)	0.06	159
							Subtotal: 652
337-412(ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	157
<337	Model 4 [5]	1.00	1.06 (0.60 - 1.90)	1.34 (0.76 - 2.38)	0.79 (0.45 - 1.40)	0.40	320
≥412	Model 4 [5]	1.00	0.86 (0.44 - 1.66)	0.84 (0.43 - 1.62)	0.59 (0.30 - 1.14)	0.12	158
							Subtotal: 635
				Animal-sourced pattern			

337-412(ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	197
<337	Model 1 [2]	1.00	1.48 (0.90 - 2.43)	1.14 (0.70 - 1.86)	1.09 (0.67 - 1.77)	0.91	391
≥412	Model 1 [2]	1.00	1.15 (0.65 - 2.05)	0.96 (0.54 - 1.68)	1.05 (0.60 - 1.84)	0.97	196
							Subtotal: 784
337-412(ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	164
<337	Model 2 [3]	1.00	1.35 (0.78 - 2.36)	1.24 (0.72 - 2.14)	1.21 (0.69 - 2.11)	0.78	329
≥412	Model 2 [3]	1.00	1.27 (0.66 - 2.46)	1.16 (0.61 - 2.21)	1.60 (0.84 - 3.03)	0.24	159
							Subtotal: 652
337-412(ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	164
<337	Model 3 [4]	1.00	1.35 (0.78 - 2.36)	1.24 (0.72 - 2.14)	1.22 (0.70 - 2.12)	0.76	329
≥412	Model 3 [4]	1.00	1.27 (0.66 - 2.46)	1.16 (0.61 - 2.21)	1.61 (0.85 - 3.07)	0.23	159
							Subtotal: 652
337-412(ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	157
<337	Model 4 [5]	1.00	1.22 (0.69 - 2.15)	1.22 (0.69 - 2.13)	1.17 (0.66 - 2.07)	0.76	320
≥412	Model 4 [5]	1.00	1.18 (0.60 - 2.29)	1.15 (0.59 - 2.23)	1.57 (0.81 - 3.02)	0.23	158
							Subtotal: 596
				Plant-sourced pattern			
337-412(ref)	Model 1 [2]	1.00	1.00	1.00	1.00	-	197
<337	Model 1 [2]	1.00	1.19 (0.72 - 1.95)	0.89 (0.54 - 1.46)	1.01 (0.63 - 1.63)	0.88	391
≥412	Model 1 [2]	1.00	1.52 (0.85 - 2.72)	1.67 (0.95 - 2.94)	1.05 (0.59 - 1.90)	0.96	196
							Subtotal: 784
337-412(ref)	Model 2 [3]	1.00	1.00	1.00	1.00	-	164
<337	Model 2 [3]	1.00	0.96 (0.55 - 1.70)	0.70 (0.39 - 1.24)	0.84 (0.48 - 1.47)	0.42	329
≥412	Model 2 [3]	1.00	1.29 (0.66 - 2.54)	1.09 (0.56 - 2.13)	0.88 (0.45 - 1.75)	0.42	159

							Subtotal: 652
337-412(ref)	Model 3 [4]	1.00	1.00	1.00	1.00	-	164
<337	Model 3 [4]	1.00	0.97 (0.55 - 1.71)	0.69 (0.39 - 1.23)	0.84 (0.48 - 1.46)	0.40	329
≥412	Model 3 [4]	1.00	1.30 (0.66 - 2.56)	1.08 (0.55 - 2.12)	0.88 (0.44 - 1.74)	0.40	159
							Subtotal: 652
337-412(ref)	Model 4 [5]	1.00	1.00	1.00	1.00	-	157
<337	Model 4 [5]	1.00	1.03 (0.58 - 1.83)	0.76 (0.42 - 1.37)	0.92 (0.52 - 1.62)	0.63	320
≥412	Model 4 [5]	1.00	1.37 (0.69 - 2.71)	1.18 (0.59 - 2.35)	0.94 (0.47 - 1.89)	0.54	158
							Subtotal: 635

[1]P for trend was calculated using the median value of the factor score by the quartiles of intakes of each pattern
[2] Model1 adjusted for age.
[3] Model2 further adjusted for education, smoking, stand drinks, physical activity and shift work.
[4] Model3 further adjusted for waist circumference.
[5] Model4 further adjusted for fasting glucose, LDL cholesterol, HDL cholesterol and systolic blood pressure.
TST, total sleep time.

Appendix E. Supplemental Table 6.4 from study in Chapter 6

Supplemental Table 4 Associations (Odds ratio (OR) 95%CI) between quartiles of the nutrient patterns and self-reported sleep symptoms

Self-reported sleep symptoms	Quartiles of nutrient patterns					n
	Q1 (n = 372) ref	Q2 (n = 372)	Q3 (n = 372)	Q4 (n = 372)	P for trend[1]	
Daytime sleepiness						
Vitamin B & Folate						
Model 1	1.00	1.08 (0.86 - 1.36)	1.07 (0.85 - 1.34)	1.04 (0.83 - 1.31)	0.75	1,487
Model 2	1.00	1.16 (0.90 - 1.50)	1.11 (0.86 - 1.43)	1.11 (0.86 - 1.42)	0.55	1,257
Model 3	1.00	1.15 (0.89 - 1.48)	1.10 (0.85 - 1.41)	1.09 (0.85 - 1.40)	0.61	1,257
Model 4	1.00	1.14 (0.88 - 1.48)	1.08 (0.83 - 1.39)	1.07 (0.82 - 1.38)	0.79	1,222
Animal-sourced pattern						
Model 1	1.00	0.95 (0.76 - 1.20)	1.19 (0.95 - 1.48)	1.00 (0.79 - 1.26)	0.66	1,487
Model 2	1.00	0.99 (0.77 - 1.28)	1.15 (0.90 - 1.47)	1.02 (0.79 - 1.32)	0.58	1,257
Model 3	1.00	0.98 (0.76 - 1.26)	1.15 (0.91 - 1.47)	1.01 (0.78 - 1.30)	0.67	1,257
Model 4	1.00	0.99 (0.76 - 1.28)	1.15 (0.90 - 1.47)	0.99 (0.76 - 1.29)	0.78	1,222
Plant-sourced pattern						
Model 1	1.00	1.03 (0.83 - 1.30)	0.93 (0.74 - 1.18)	1.05 (0.84 - 1.31)	0.83	1,487
Model 2	1.00	1.02 (0.79 - 1.31)	0.98 (0.75 - 1.27)	1.04 (0.80 - 1.34)	0.82	1,257
Model 3	1.00	1.01 (0.79 - 1.31)	0.98 (0.75 - 1.27)	1.05 (0.81 - 1.35)	0.75	1,257
Model 4	1.00	1.01 (0.78 - 1.30)	0.98 (0.75 - 1.28)	1.05 (0.81 - 1.36)	0.72	1,222

Poor sleep quality						
Vitamin B & Folate						
Model 1	1.00	1.09 (0.80 - 1.47)	1.00 (0.73 - 1.36)	1.20 (0.89 - 1.62)	0.75	751
Model 2	1.00	1.18 (0.84 - 1.67)	1.10 (0.78 - 1.55)	1.26 (0.89 - 1.77)	0.55	622
Model 3	1.00	1.20 (0.85 - 1.69)	1.11 (0.78 - 1.56)	1.27 (0.90 - 1.79)	0.61	622
Model 4	1.00	1.23 (0.86 - 1.75)	1.16 (0.81 - 1.65)	1.31 (0.92 - 1.86)	0.79	606
Animal-sourced pattern						
Model 1	1.00	1.12 (0.84 - 1.50)	0.97 (0.72 - 1.31)	0.94 (0.69 - 1.27)	0.66	751
Model 2	1.00	1.11 (0.79 - 1.55)	1.01 (0.72 - 1.41)	0.93 (0.66 - 1.31)	0.58	622
Model 3	1.00	1.11 (0.79 - 1.55)	1.01 (0.72 - 1.41)	0.94 (0.67 - 1.32)	0.67	622
Model 4	1.00	1.14 (0.81 - 1.61)	1.02 (0.72 - 1.43)	0.95 (0.67 - 1.34)	0.78	606
Plant-sourced pattern						
Model 1	1.00	0.99 (0.73 - 1.33)	0.95 (0.71 - 1.28)	0.94 (0.69 - 1.26)	0.83	751
Model 2	1.00	1.09 (0.78 - 1.54)	1.11 (0.78 - 1.57)	1.05 (0.74 - 1.48)	0.82	622
Model 3	1.00	1.10 (0.78 - 1.55)	1.10 (0.78 - 1.56)	1.04 (0.74 - 1.47)	0.75	622
Model 4	1.00	1.06 (0.75 - 1.50)	1.06 (0.74 - 1.52)	1.01 (0.71 - 1.43)	0.72	606

[1]P for trend was calculated using the median value of the factor score by the quartiles of intakes of each pattern
[2] Model1 adjusted for age.
[3] Model2 further adjusted for education, smoking, stand drinks, physical activity and shift work.
[4] Model3 further adjusted for waist circumference.
[5] Model4 further adjusted for fasting glucose, LDL cholesterol, HDL cholesterol and systolic blood pressure.