Using the Network Approach to Psychopathology to Better Understand the Complex Relationships between Depressive Symptoms with Risk Factors, Suicidality, and Inflammation amongst Pacific Young People in New Zealand

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Dedication

To my dear faithful companion Grover who kept me sane during my many hours in the home office. Here's to many more analyses and walks together (sorry Rua, if I do another PhD, I'll dedicate it to you)

Abstract

Depression is the leading cause of disability worldwide and is closely associated with suicidality (suicidal thoughts, plans or attempts), many serious physical health conditions, and actual suicide. Depression, and suicide are problems in New Zealand (NZ), which has higher depression prevalence and teen suicide rates than many similar high-income countries. Within NZ, the burden of depression and suicidality is disproportionate, affecting some groups more than others. Pacific adolescents and Pacific young adults in NZ show significantly higher rates of depressive symptoms, psychological distress and suicidality compared to NZ European adolescents. Despite these elevated risks little research has been conducted into depression and suicidality amongst this population.

This thesis applied the network approach to psychopathology to investigate various aspects of depressive symptomatology amongst NZ Pacific adolescents and young adults, specifically associations between individual depression symptoms with risk factors, suicidality and inflammation. According to the network perspective, the symptoms and their interactions comprise the disorder rather than being manifestations of a common cause. Using this approach, depression is measured in terms of individual symptoms (although it may also be measured complementarily in other ways) and the associations amongst the individual depression symptoms and between the symptoms and other relevant non-symptom factors are visualized in a highly intuitive network graph. The overall aim of this thesis was to use the network approach, to gain a deeper insight into these complex and multi-faceted relationships.

To fulfil this objective, three original studies and a literature review were conducted. The first part of this thesis focused primarily on associations between psychosocial risk factors with depression and suicidality, with two original studies. One study investigated associations between depression symptoms with a wide range of multi-dimensional potential risk factors for depression. The second study was an in-depth investigation into associations between suicidality with individual depression symptoms and self-harm. Both studies broke new ground being the first time that the network approach had been used to investigate depression risk factors or suicidality amongst Pacific adolescents in NZ. The second part of the thesis moved to investigate possible biological correlations with depression and specifically focused on the inflammation - depression relationship. This included conducting a literature review and an original study into associations between depression and inflammation amongst Pacific young adults. The original study represented the first time that links between depression and inflammation had been examined for Pacific New Zealanders of any age.

The results were illuminating. Measuring depression in terms of individual symptoms and the additional statistical acuity derived from analysing network topology revealed a more nuanced

and dynamic understanding of the relationships under study, which also revealed potentially culturally shaped findings. The results from the original studies also suggested possible targets for clinical interventions and information that could be used to shape prevention strategies and treatment plans. Overall, the primary hope from this thesis is that the information obtained has clinical usefulness, which will aid the treatment of depression and suicidality amongst Pacific young people. Secondarily, it aims to add empirical weight to calls for re-evaluation of the prevailing ways depression is measured, including within research frameworks, clinical environments, and education and health settings.

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List of Abbreviations

AUT	Auckland University of Technology
AUTEC	Auckland University of Technology Ethics Committee
BDI	Beck Depression Inventory
BDI-FS	Beck Depression Inventory Fast Screen
BDI-II	Beck Depression Inventory Version two
BIC	Bayesian Information Criterion
BMI	Body mass index
CBCL	Child Behavior Checklist
CDI:S	Children's Depression Inventory Short Version
CE	Cultural Efficacy
CFA	Confirmatory factor analysis
CFI	Comparative fit index
COVID- 19	Coronavirus disease 2019
CRP	C-reactive protein
PRS	Polygenic risk scores
CS	Correlation stability
CV	Cross validation
CVD	Cardiovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders version four
DTW	Does things wrong
EBIC	Extended Bayesian Information Criterion
GME	Group Membership Evaluation
GSA	Green space availability
HPA	Hypothalamic-pituitary-adrenal
IL-6	Interleukin 6
IMD	Immuno-metabolic depression
IQR	Interquartile range
KS	Kolmogorov-Smirnov
LASSO	Least absolute shrinkage and selection operator
MAR	Missing at Random
MCAR	Missing Completely At Random
MDD	Major Depressive Disorder
MGMs	Mixed graphical models
MNAR	Missing Not at Random

MSE	Mean squared error
NEF	Not enough friends
NOW	Not work out
NRMSE	Normalized root mean squared error
NZ	New Zealand
NZiDep	New Zealand index of socioeconomic deprivation for individuals
OECD	Organisation for Economic Co-operation and Development
OOB	Out-of-the-bag
OR	Odds ratio
PCB	Pacific Connectedness and Belonging
PDD	Persistent Depressive Disorder
PFC	Proportion falsely classified
PIF	Pacific Islands Families
PIR	Probability inclusion rate
RCE	Religious Centrality and Embeddedness
RMSEA	Root mean squared error of approximation
SD	Standard deviation
SRMR	Standardized root mean square residual
SST	Serum Separator Tubes
TLI	Tucker Lewis Index
TNF-a	Tumour necrosis factor alpha
WHO	World Health Organization
YSR	Youth Self-Report

Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor used artificial intelligence tools or generative artificial intelligence tools (unless it is clearly stated, and referenced, along with the purpose of use), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

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Quote

“When I look at the vast, intricate networks that form our reality, I can’t help but feel awe for the mysterious way everything is connected,” Albert-László Barabási, physicist and network scientist.

Prelude to Chapter 1

This chapter introduces the main elements that informed the thesis: depression and suicidality amongst Pacific young people in NZ and the network approach to psychopathology. It identifies the gaps in relevant literature and gives an outline of the thesis chapters and the contributions to knowledge.

Chapter 1. Depression and Suicidality amongst Pacific Young People and the Network Approach to Psychopathology

1.1. Facts about Depression

Depressive disorder is a debilitating disease, with globally around 5% of adults (defined as 20 years and over) suffering from depression (World Health Organization (WHO), 2023). It is the leading cause of disability worldwide (WHO, 2017). It is closely associated with poor physical health, such as higher risk of cardiovascular disease (CVD) (Bradley & Rumsfeld, 2015), co-morbid with substance abuse (Calarco & Lobo, 2021; Erfan et al., 2010) and anxiety (Pollack, 2005), and makes it harder to work, study or form quality relationships (WHO, 2023). A recent study with a large cohort of over 200,000 found that depression was linked to the development of dementia, and the link remained irrespective of whether depression was diagnosed in early, middle, or later in life (Elser et al., 2023). It also has a huge economic impact and is estimated to cost the global economy around US$1 trillion each year and this figure is estimated to rise to a staggering US$16 trillion by 2030 (Chodavadia et al., 2023). When depression occurs in young people, it can cast a long shadow. It has the potential to have a long term, negative impact on earnings, and is comorbid with other medical conditions, substance abuse and suicide (Armstrong & Costello, 2002; Goodman et al., 2011; Keenan-Miller et al., 2007). For approximately 75% of adults with long-term mental health conditions, the onset of symptoms occurred before the age of 24 (Barker et al., 2019), and the peak periods for depression onset are adolescence and young adulthood (Kessler et al., 2007; Weissman et al., 1996). The WHO (2020) estimates that around 3% of 15-19 years olds suffer from depressive disorder, and 14% of 10–19-year-olds experience mental health conditions that are largely unrecognized and untreated.

1.2. Depression, Suicidality, Self-harm, and Suicide

Depression is highly comorbid with suicidal thoughts, suicidal plans, suicide attempts (compositely termed in this thesis as suicidality), and self-harm and actual suicides. A study found that over two-thirds of those with suicide ideation had a mental health disorder and out of these, depressive disorder was the strongest predictor of suicide ideation, although in this study, it less strongly predicted suicide plans and attempts (Nock et al., 2010). Another study found that depressive disorder was the most common mental health disorder to be comorbid with both self-harm (termed deliberate self-harm) and actual suicides (Haw et al., 2002). What is clear is that the association between depression and suicide ideation has consequential effects, as suicide ideation predicts suicide plans, attempts and actual suicide (Coppersmith et al., 2017;

Franklin et al., 2017), including amongst adolescents (Goldston et al., 1999; Horwitz et al., 2015). Self-harm has been found to be consistently associated with suicidality and actual suicides, particularly in adolescence (Bilsen, 2018; Galaif et al., 2007; Goldston et al., 1999; Macalli et al., 2021), including in a large meta-analysis (Gillies et al., 2018). Furthermore, the association strengthens as incidences of self-harm increase (Gillies et al., 2018).

1.3. Depression, Suicidality, and Suicide in New Zealand

Depression, suicidality and suicide are particular problems in New Zealand (NZ). In an international survey, NZ had the fourth highest 12-month depression prevalence rate (6.6%) out of all the countries surveyed (high income and low-middle income), and the second highest out of the high-income countries (Kessler & Bromet, 2013). NZ had the highest teen (aged 15-19) suicide rate in the Organisation for Economic Co-operation and Development (OECD), in a 2017 report (OECD, 2017). Overall, within NZ, those aged 15-24 have the highest suicide rate, at 20.4 (per 100,000 people), which is almost double the rate of the age group with the lowest (65 years plus) (The Treasury, 2022). Tragically, the situation is worsening. Depression symptom severity, thoughts of suicide, and suicide attempts showed significant increases from 2012 to 2019 amongst NZ adolescents. The percentage of those NZ adolescents with significant depression symptoms (symptoms severe enough to disrupt ability to function) rose from 13% in 2012 to 23% in 2019, those with suicidal thoughts rose from 15% to 21%, and self-reported suicide attempts rose from 4% to 6% (Sutcliffe et al., 2023). A recent report found that young people in NZ (aged 15-24) were especially impacted by psychological (mental) distress[1], expressed by showing symptoms of anxiety, depression, or psychological fatigue, with over 20% reporting that they experienced high or very high levels of psychological distress (Ministry of Health, 2023). The Ministry of Health 2022 report showed that psychological distress had risen rapidly from 2011/12, when only 5.1% reported experiencing such high levels (Ministry of Health, 2022). The COVID-19 pandemic played a role in this rise globally (WHO, 2022), including in NZ (Siegert et al., 2023), but the trend had been increasing over time pre-pandemic, particularly amongst adolescents and young adults. A recent investigation into youth mental

[1] Psychological distress (aged 15+ years) is measured using The Kessler Psychological Distress Scale (K10). A K10 score of 12 or more is strongly associated with having a mental (depressive or anxiety) disorder (Kessler et al 2003). Psychological distress is measured using symptoms of depression, anxiety, and psychological fatigue in the past four weeks (Kessler et al 2003) and it is the self-report measure used by the Ministry of Health when assessing mental health through their annual surveys (Ministry of Health (2022) . It is used here (instead of depression) as the most up to date statistics are available for psychological distress rather than for depression, however, depression is highly co-morbid with both anxiety and fatigue, and so very likely to follow the same upward trend (Corfield et al., 2016; Pollack, 2005).

health referred to NZ adolescents as experiencing a “mental health pandemic” (Menzies et al., 2020, p3).

1.4. Mental Health of Pacific New Zealanders – Adolescents and Young Adults

Within NZ, depression affects some groups disproportionately. A report into Pacific mental health and wellbeing in NZ found that the severity of psychological distress was significantly higher in Pacific people compared to Others[2] (a composite ethnic group that excludes Pacific people and Māori), and amongst Pacific people in the NZ the prevalence of medium to high levels of psychological distress was highest for young Pacific people aged 15-24 years, at 38% (Health Promotion Agency, 2018). Pacific adolescents in NZ also show significantly higher rates of depressive symptoms, suicidal thoughts, and suicide attempts compared to NZ European adolescents, with prevalence rates for significant depressive symptoms of 25% compared to 20%, suicidal thoughts at 26% compared to 18%, and self-reported suicide attempts at 12% compared to 3% (Sutcliffe et al., 2023). In a cluster analysis of NZ adolescents based on mental health indicators, five clusters were identified, including a severe cluster with the least positive mental health, based on the indicators used. Pacific adolescents (as well as Māori and those living in high deprivation areas) were overrepresented in this cluster (Sutcliffe et al., 2024).

Worryingly, despite these increased risks of mental disorders, Pacific people are less likely than other groups to seek medical help for depression (Tucker-Masters & Dr Tiatia-Seath, 2017). It was assumed that Pacific people had lower rates of mental illness compared to other groups, as they were less likely to seek help medically and statistics used were based on clinical diagnoses (Tucker-Masters & Tiatia-Seath, 2017). However, a groundbreaking study in 2006 and subsequent reports have showed this is not the case and that Pacific people have worse rates of mental health compared to Others, and particularly amongst adolescent and young adult Pacific populations (Health Promotion Agency, 2018; Ministry of Health, 2006). In terms of a clinical diagnosis, their depression is often under-diagnosed (Lee et al., 2017), and research found that only 25% of Pacific New Zealanders with a severe mental disorder sought help through a mental health service compared to 58% for New Zealanders overall (Fa’alogo-Lilo & Cartwright, 2021).

[2] Māori are also disproportionately likely to report significant depressive symptoms, suicidal thoughts, and attempted suicide, and whilst this is also of concern Māori are not the focus of the present research.

1.4.1. Pacific People in NZ

The depression and suicidality statistics for Pacific New Zealanders sit in contrast with the vibrancy and cultural richness Pacific people contribute to NZ. The Pacific population in NZ is young, with a median age of 23 years compared with 38 years for NZ as a whole (Stats NZ, 2018). It comprises those whose heritage traces back to various Pacific islands, with the largest groups from Samoa (48%), Tonga (22%), and the Cook Islands (21%), but also including Fiji, Niue, Tokelau, Kiribati, and Tuvalu. Originally the foundation of Pacific settlement was through migration, although in the present day over 60% of Pacific New Zealanders are born in NZ (Thomsen et al., 2023). Around 9% of the NZ population identify as being of Pacific heritage (Stats NZ, 2023). They are highly urbanized with over 64% residing in Auckland region, 11% in Wellington region, and 5% equally in Waikato and Canterbury regions (Ministry for Pacific Peoples, 2020). They contribute much to the NZ economy in many ways, including but not limited to their contributions to the health sector, with 4% of all nurses in NZ identifying as Pacific (Ministry for Pacific Peoples, 2020), and to music, art, and culture, including their celebrations of pan-Pacific culture through the festivals Polyfest, which also celebrates Māori culture, and Pasifika Festival (Ministry for Pacific Peoples, 2022). Unfortunately, Pacific New Zealanders experience socio-economic deprivation at above average levels; they are over-represented in the Auckland's poorest suburbs (Ministry of Health, 2021), and a recent survey found that 37% of Pacific children live in severe to moderate food insecure households compared to 19% for NZ children overall (Ministry of Health, 2019).

1.4.2. Depression and Suicidality amongst NZ Pacific Young People – review of literature

Despite their elevated risks for depression and suicidality, few studies have investigated depression and suicidality amongst Pacific adolescents and young adults, with some exceptions. Paterson et al. (2018) examined cultural, individual, and familial risk and protective factors for depression amongst Pacific adolescents (aged 11 and at 14) and found significant cross-sectional risk factors at ages 11 and 14 were being a bullying victim or perpetrator and gang involvement; protective factors were positive parenting, and Tongan heritage. At age 11, higher externalizing behaviour scores (rule-breaking and aggressive behaviour), measured by the Child Behavior Checklist (CBCL) (Bordin et al., 2013), were risk factors and mother being tertiary educated was protective. At age 14, higher internalizing behaviour scores on the CBCL (anxious/ depressed, withdrawn/ depressed, and somatic complaints) was a risk factor, as was being female (Paterson et al., 2018). Other research has analysed associations between depression and discrete aspects of behaviour or environment. One studied the relationship between sleep and depressive symptomology amongst Pacific adolescents and found that insufficient sleep was associated with higher levels of depressive symptoms (McLay et al., 2023). Another examined the perceptions of neighbourhood safety and green space availability

(GSA) and found that certain groups (Pacific, Asian, disabled, and those from gender and sexual minorities) felt less safe in their neighbourhoods, had lower emotional well-being, and higher depressive symptoms compared to other groups (Zhang et al., 2024).

Teevale et al. (2016), found that among Pacific adolescents in NZ, the likelihood of a suicide attempt was associated with being female, experiencing food insecurity, weak family connections and inadequate monitoring, dissatisfaction with life, having a religious affiliation, and having a family member or friend who had attempted or died by suicide. However, stronger family monitoring was identified as a protective factor. Of those who had made a suicide attempt, 71% had also experienced suicide ideation and self-harm (Teevale et al., 2016). Another study, using data from Pacific adolescents arriving at hospital after a suicide attempt, found that significant triggers for these attempts were stress related to family or relationship conflict (Aoelua, 2018). Neither of these studies on suicidality (Teevale et al., 2016; Aoelua, 2018) included a measure for depression, so its impact on suicidality was not measured. A large study of New Zealanders aged 10-29 years (mean age 21) found that the odds of presenting at hospital for self-harm decreased the further they were from an alcohol outlet and found this to be true after controlling for ethnicity, although this study did not specifically investigate this for ethnic groups separately (Hetrick et al., 2024). Another study with young people in NZ aged 10-24, again not specific to Pacific adolescents, found that self-harming was less likely in health promoting environments, defined as those with green spaces, blue spaces, physical activity facilities, fruit and vegetable outlets, and supermarkets, compared to health constraining environments, defined as those with fast-food outlets, takeaway outlets, dairy outlets and convenience stores, alcohol outlets, and gaming venues (Hetrick et al., 2024).

1.5. Depression is Complex and Highly Heterogeneous

Depression is complex and highly heterogeneous in terms of risk factors, prognosis, and duration (Dobson & Dozois, 2011; Lorenzo-Luaces, 2015; Mullarkey et al., 2019; Thapar et al., 2012). It is multi-factorial and contextually driven and thought to be the result of complicated interrelationships between several risk factors (Dobson & Dozois, 2011; Maughan et al., 2013). In a book on risk factors for depression, for example, the authors identified 18 highly plausible, 29 plausible, and 17 possible risk factors (Dobson & Dozois, 2011). In a review of 134 meta-analyses investigating the causes and risk factors for depression, over 100 associations were nominally identified as potential risk factors, before applying various tests of robustness (Köhler et al., 2018). Adding to these complications is the highly heterogeneous nature of symptom presentations across individuals, groups and time. Fried & Nesse (2015a) reviewed symptom presentations in a large sample (N=3703) of depressed subjects who met the diagnostic criteria

for Major Depressive Disorder (MDD)[3] and found over 1000 unique symptom profiles, with the most frequent symptom cluster being endorsed with less than 2% frequency. Complicating matters further, risk and protective factors for depression and symptom presentations have been found to differ by gender, race, ethnicity, and culture, and through interactions between these characteristics. Bailey et al. (2019) found, for example, that job security was more protective against depression in African American men than for White or Hispanic people. The same study identified that self-perceived racial discrimination was damaging for mental health for both African American men and women but was more so for African American women (Bailey et al., 2019). Another study discovered that there were racial and ethnic differences in prevalence rates for types of depression, with White Americans more likely to have lifetime prevalence rates of MDD, and African Americans and Mexican Americans higher lifetime prevalence rates of dysthymic disorder (or Persistent Depressive Disorder (PDD))[4] (Riolo et al., 2005).

1.6. Insufficient Progress in Understanding, Diagnosing and Treating Depression

Although there have been advancements in terms of depression theories and depression models, which have enhanced understanding (Dobson & Dozois, 2011; Li et al., 2021a), it is still misdiagnosed and difficult to treat and our understanding of its pathophysiology and how to effectively treat it is still insufficient (Fried et al., 2022; Holtzheimer & Mayberg, 2011). Research found that in general practice, often the first port of call of those suffering depressive symptoms, only around half of those with MDD received a diagnosis of it (van Rijswijk et al., 2009), and there exists much clinical variability around what qualifies as a depression diagnosis. A study found that agreement amongst clinicians for MDD diagnoses had "questionable" reliability, based on a common measure of inter-rater reliability, the Kappa coefficient (Cohen, 1960) (Xiaohua & Jiang, 2016). There also exists a large proportion of depressed people for whom anti-depressants do not work effectively. It is estimated that around a third of depressed people do not respond to anti-depressant treatments, termed treatment resistant depression (TRD) (McIntyre et al., 2023). Meta-analyses and aggregation of data from multiple studies

[3] Major Depressive Disorder (MDD), also referred to as clinical depression, is a clinical diagnosis of depression. For a diagnosis, a set of criteria have to be fulfilled, based on guidelines in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* (American Psychiatric Association, 2013). Depressive symptomatology is often assessed with inventories of depression symptoms and can be self-reported. The term depression is used here to cover both forms.

[4] With MDD depressive episodes and severity of symptoms are usually more severe than with Persistent Depressive Disorder (PDD), but with PDD the symptoms are more persistent.

indicate that anti-depressants only outperform placebos for the most severe cases of MDD (Lorenzo-Luaces, 2015).

These difficulties in diagnosing and treating depression have motivated a search for depression biomarkers, which has led to low-grade, chronic inflammation being implicated as a potential biomarker for depression, and a contributor to its pathophysiology (Raison et al., 2006; Raison & Miller, 2011), supported by several large meta-analyses (e.g. Dowlati et al., 2010; Howren et al., 2009; Osimo et al., 2019). However, these meta-analyses also had high levels of heterogeneity, and many individual studies have not found any associations between depression and inflammation (e.g. Bizik et al., 2014; Steptoe et al., 2003) or have found a negative relationship between inflammatory biomarkers and depression (Schmidt et al., 2016). There is a growing acceptance that certain subgroups of depressed people exhibit elevated inflammation (Berk et al., 2013; Osimo et al., 2019; Raison & Miller, 2011), but what characterises them is still an area of active research. There are a number of biomarker areas which show promise as objective biological identifiers of depression or depression subtypes or a depression phenotype, including but not limited to inflammatory markers (e.g. C-reactive protein (CRP), interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF-a)), and over the last 50 plus years scientists and researchers have proposed numerous biological causes and markers for depression and explanations as to why treatment response varies (Callahan & Berrios, 2005). However, there is still no overall agreement of the biology of depression or a biological pathway for all depressed people (Callahan & Berrios, 2005; Fried et al., 2022), and different biological mechanisms could underpin the varied symptom presentations (Lamers et al., 2020).

1.7. Depression Measurement

Despite the highly heterogeneous nature of depression symptom profiles (for example, see Fried & Nesse, 2015a; Fried & Nesse, 2015b), the predominant methods used for diagnosing and measuring it are largely reductionist and do not capture this variability. Some researchers believe that this failure to capture the different ways in which depression presents itself is slowing or even holding back progress (Fried, 2015a; Fried et al., 2022; Lux & Kendler, 2010). The most common method for assessing and quantifying the severity of depression amongst community populations is by summing symptom scores from self-reported depression instruments (which are comprised of inventories of symptoms, such as the Beck Depression Inventory (BDI) (Beck et al., 1996)) together to create a sum score (Borsboom & Cramer, 2013; Fried et al., 2014). Symptom severity on these inventories is usually assessed using scores on a Likert scale, with higher scores denoting higher endorsement of that symptom, after applying any necessary reverse coding. Then, either this sum score is used as way to quantify depression severity or one or more cutoffs are applied to the total scores to delineate depressed from not depressed persons or, amongst depressed persons, different categories of severity.

A commonly used method to diagnose depression clinically is through the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000), with versions being periodically updated. For a diagnosis of MDD, nine symptoms are listed in the DSM-V and five or more must be present for the past two weeks and represent a change from previous functioning, and at least one of the five must be depressed mood or loss of pleasure (American Psychiatric, 2000). Both these methods (sum score of symptoms or clinical diagnosis) can obscure the diverse nature of depression and lead to a loss of valuable information about symptom profiles (Fried & Nesse, 2015a; Fried & Nesse, 2015b).

These methods for measuring depression are based on the common cause model, which operates on the basis that symptoms are manifestation of an underlying cause, and depression is conceptualised as a latent construct. This view of depression treats symptoms as interchangeable and independent, and assumes depression is a consistent syndrome, but research has shown this not the case (Fried & Nesse, 2015a). Diagnosing via the DSM-V involves some symptom hierarchy, as endorsing depressed mood or loss of pleasure are mandatory for a diagnosis, but the other symptoms are treated as equivalent. With these methods, for example, loss of concentration is given the same weight as having suicidal thoughts, despite associations between suicidal thoughts with depression severity and actual suicide (Beghi et al., 2013; Hawton et al., 2013).

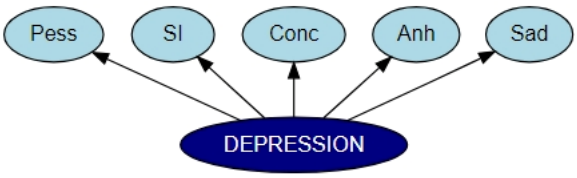

Figure 1 The common cause model of depression whereby symptoms are the manifestations of an underlying cause

(Legend: Pess=pessimism, SI= Suicide ideation, Conc= Concentration difficulties, Anh = Anhedonia, Sad = Sadness)

1.7.1. The Differential Impact of Individual Depression Symptoms

Depression dimensions, based on summing subscales of symptoms (two common ones being psychological (also termed cognitive) and somatic dimensions (also termed neurovegetative)), and depression subtypes, such as atypical and melancholic depression, with clinical profiles of symptom endorsement in depression manuals such as the DSM-V (American Psychiatric Association, 2013) were created to ameliorate the problems with the variability of symptom constellations amongst depressed people. However, they are not able to fully encapsulate the

diversity of symptom presentations, and many studies have found when studying depression in terms of individual symptoms that the results were highly symptom specific. Lux and Kendler (2010) found that symptoms on the DSM-IV (an earlier version of the manual from the DSM-V) differed widely in terms of associations with risk factors, and the variance was only partly explained by two common depression dimensions (termed cognitive and neuro-vegetative in this study) (Lux & Kendler, 2010).

Compounding this problem is that there are no standardised measures of what constitutes somatic and psychological depression dimensions, in terms of what symptoms should be included (Majd et al., 2020). Furthermore, a large meta-analysis failed to find conclusive evidence of the existence of depressive subtypes or dimensions (Van Loo et al., 2012). The impact of depression symptoms on impairment varies significantly (Fried & Nesse, 2014), and depression can be severe, even if only one or two symptoms are present. Although depression and suicide are strongly associated, the impact of individual depression symptoms on suicide has been found to be extremely variable. Beck et al. (1985) found that the pessimism item of the Beck Depression Inventory (BDI) (Beck et al., 1961) predicted suicide deaths more accurately than a sum score of depression symptoms.

This variability in depression symptom presentation could be underlaid by different biological mechanisms and markers, and it is argued that the inability of prevailing depression measurement methods to capture the diversity of symptom profiles is at least partially responsible for a lack of advancement in discovering reliable depression biomarkers (Fried & Cramer, 2017; Fried et al., 2022; Fried et al., 2020; Lynch et al., 2020). Supporting this view, associations between inflammatory biomarkers and depression have also been found to be symptom specific (e.g. Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016; Lamers et al., 2018; Milaneschi et al., 2021), and some researchers advocate for more nuanced ways of measuring depression, including in terms of individual symptoms (Fried & Cramer, 2017; Fried et al., 2022; Fried et al., 2020; Lynch et al., 2020).

1.8. The Network Approach to Psychopathology

1.8.1. An Alternative Way to Conceptualise Mental Disorders and Conditions

An alternative way to conceptualise mental disorders, including depression, which addresses depression heterogeneity is the network approach to psychopathology. According to this approach, the symptoms and their causal interactions constitute the disorder rather than being passive manifestations of a common cause or latent construct, as is the assumption with the latent variable approach (Borsboom, 2017; Borsboom & Cramer, 2013). This approach conceptualises mental disorders as dynamic systems, leveraging ideas from network science,

where elements of the system can contaminate other elements that they are connected to (Barabási, 2012). The network approach to psychopathology utilises tools developed from graph theory (Lauritzen, 1996) to create networks of symptoms, and increasingly relevant non-symptom factors, and plots these as a complex system of interacting components, which can be depicted with a network graph (a simple depiction of a network graph is shown in Figure 2). (Borsboom, 2017; Borsboom & Cramer, 2013; McNally, 2016).

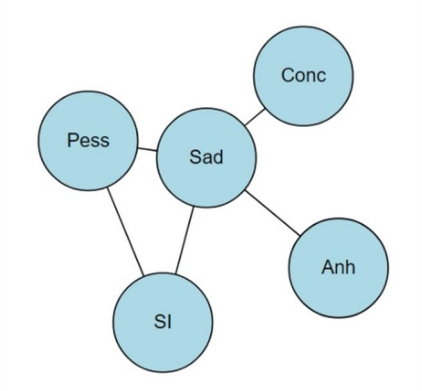

Figure 2 The network approach conceptualises mental disorders as networks of interacting symptoms

Legend: Pess= Pessimism, Sad= Sadness, Conc= Concentration difficulties, Anh= Anhedonia, SI= Suicide ideation

In psychological networks, nodes represent the symptoms of a disorder or condition and other relevant variables and edges the conditional pairwise relationships between them. Conditional in this sense means that an edge between two nodes is not the result of other network nodes as their potential influence on this edge has been accounted for (Borsboom et al., 2021; Haslbeck & Waldorp, 2020). Network analysis is a way of empirically quantifying these relationships. The use of networks to model psychological data has soared in the last decade, largely due to the work of pioneers of the network approach, the development network theories of psychopathology (Borsboom, 2008; Borsboom, 2017; Borsboom & Cramer, 2013; Cramer et al., 2010; Fried & Nesse, 2014; Van Der Maas et al., 2006) and software packages that have made fitting these networks easier (Epskamp, 2020; Epskamp et al., 2018; Epskamp et al., 2012; Haslbeck et al., 2019; Haslbeck, 2022; Haslbeck & Waldorp, 2020).

Although it may appear that the latent variable approach and the network approach to psychopathology are exclusionary, it is also argued that the two approaches can, in fact, complement each other (Epskamp et al., 2017; Guyon et al., 2017). Symptoms and other non-symptom factors may co-occur because of an underlying mechanism, characteristic, or biological trait, which the network approach could help discover (Guyon et al., 2017). The

suitability of using the network approach or the latent variable approach or both may depend on whether the assumptions of the common cause model hold (Borsboom, 2022) and the questions the researcher is attempting to answer. The network approach offers a promising addition to more traditional ways of understanding the psychopathology of mental disorders, and the approach does provide compelling evidence for a focus on relationships between symptoms, rather than just syndromes (Bringmann & Eronen, 2018), although the two could be combined within one network, as shown by Epskamp et al. (2017).

1.8.2. Advantages of the Network Approach

As a graphical method, a major advantage of using network analysis is the highly interpretable way interactions between variables in the network are displayed, making it a powerful and intuitive visualization tool. Network analysis also facilitates additional parameters to be discerned, that would not be possible with more traditional methods, such as regression, as analysis can be conducted simultaneous at three levels of the network: macro level, meso level, and micro level (Dzwigol, 2023), and at each level network-based statistics and metrics can be calculated. At the macro level, centrality measures (Opsahl et al., 2010) and predictability statistics (Haslbeck & Waldorp, 2018) can also be used to discover the most central nodes in the network. At the meso or subnetwork level, symptom clusters within the network can be detected directly from the network graph, although there are more formal methods available, which could include the identification of symptoms which connect different symptom clusters together and could be acting as a bridge between comorbid mental conditions (Jones et al., 2021). At the micro level of the network, pairwise direct and indirect associations between variables of interest can be identified. Indirect associations may provide indications of possible mediator or moderator variables, that can then be tested more formally in further research. Where the network has a particular target variable of interest, relationships amongst the predictor variables are displayed graphically, which can provide useful information around drivers of an association or indications of confounding.

According to proponents of the network approach, the relationships depicted in the network graph and the network structure provide granular and dynamic detail at the symptom-level of a mental disorder or condition that can suggest possible targets for therapies, interventions and treatment plans (Borsboom, 2017; Borsboom & Cramer, 2013). Borsboom et al. (2021) suggest there are at least two possible ways to intervene on a symptom node. One could intervene directly on the target node, with the aim of lowering its frequency or severity and hope this will affect the node itself and any nodes it is directly connected to. Borsboom et al. (2021) provide the example of if wanting to boost offline social interaction to help reduce loneliness one could intervene on the online social interaction node, which in this research was negatively connected to the offline social interaction node, with the aim of reducing online social interactions and

boosting offline social interactions. A second way is to target the link between nodes. If there is a tendency to engage in online social interaction, for example, when the person is feeling agitated or pessimistic, which could be shown in the network by a connecting edge, then one could aim to target the intervention when specifically these feelings are in play and so disrupt the network (Borsboom et al., (2021). In cross-sectional networks the temporal order of an association cannot be proven, but one can get indications of causality from conditional independencies that can then be tested in temporal networks. Networks can also provide a suitable framework for personalized treatment plans (Bringmann et al., 2013).

1.8.3. The Necessity for Diverse Ethnic/ Racial and Cultural Symptom-Level and Network Analysis

Risk factors for depression, self-harm, and suicidality have been shown to differ by race/ ethnicity and culture (Al-Sharifi et al., 2015; Bailey et al., 2019; Kirmayer, 2001; Office of the Surgeon General, 2001; Vanderwerker et al., 2007; Yen et al., 2000). Associations between possible biological correlates of depression, such as inflammatory markers, have also been shown to differ by race or ethnicity (Case & Stewart, 2014; Morris et al., 2011). Additionally, depression symptom profiles may also differ between racial/ ethnic groups, and researchers advise paying attention to the mechanisms which link race/ ethnicity to depression and to explore the cultural factors that influence the relationship (Jackson & Williams, 2006). A cross-cultural comparison of depression items on the BDI across six countries found significant differences in item scores. Significantly higher scores were found in Finland for 'changes in sleep pattern' and 'irritability', Norway for 'loss of pleasure', Mexico for 'self-criticalness', Dominican Republic for 'loss of pleasure', and Japan for 'sadness', all compared to the other countries.

Network analysis, with its measurement of depression at the symptom item level, its systems-based approach, and additional statistical measures derived from network topology, is well-placed to investigate how racial/ ethnic and cultural factors may impact depression vulnerabilities, resilience factors and symptom presentations. This is valuable insight which can inform prevention strategies, treatment plans and interventions. Network analysis findings have been shown to be sensitive to cultural and ethnic factors (Kim et al., 2021; Wasil et al., 2020). In a study of depression symptom networks of Korean children and pre-adolescents, Kim et al. (2021) found that loneliness was the most central symptom and symptoms related to school difficulties also had high centrality scores. Kim et al. (2021) posited that it may be the importance of school achievement in Korean culture and the collectivist nature of East Asian cultures which were driving these findings. Wasil et al. (2020) also found evidence that culture was influencing network structure. In a network study of Indian adolescents, feeling like a failure emerged as a central symptom, and the authors thought that the findings may be at least

partially due to the cultural pressure in India for children to live up to parents' expectations (Wasil et al., 2020). In a network analysis of associations between CRP (a marker of inflammation), depression symptoms, and measures of social relationships amongst older adults, race was found to moderate associations between depression symptoms and CRP (Lee & Min, 2023). In this study, the edge connecting raised CRP with interpersonal problems was present amongst African American participants but absent amongst White participants (Lee & Min, 2023; Li et al., 2021). Therefore, if network analysis is to fulfil its potential as an aid to depression understanding and treatment, then networks with a range of culturally and ethnically diverse populations are needed, as findings from previous studies may not be generalizable.

1.8.4. Review of Network Studies of Adolescent Depression, Suicidality and Self-harm

Several studies have used the network approach to psychopathology to explore various aspects of adolescent depression, self-harm, and suicidality, but most only in the last six years, and they have varied greatly in the extent to which they have included non-symptom risk factors. Most of the early network studies, only included symptoms of the mental disorder or condition being studied (for a review see (Robinaugh et al., 2020). Regarding adolescent depression, some studies have not included any non-symptom risk factors as their main objective was to identify the central items in networks of depression symptoms (Kim et al., 2021; Mullarkey et al., 2019) or assess network density (Schweren et al., 2018) or discover symptoms that bridged anxiety and depression (Dobson et al., 2021; Konac et al.). Others have focused on associations between depression symptoms and a narrow range of non-symptom risk factors, such as family interactions (Bodner et al., 2018), emotional and behavioural symptoms (Rouquette et al., 2018), or substance abuse (Wasil et al., 2020). A study by Boschloo et al. (2016) used network analysis to examine the network structure of 95 items on the Youth Self-Report (YSR) scale relating to emotional and behavioural problems amongst a large community sample of pre-adolescents.

With reference to adolescent suicidality, most network studies scrutinized relationships between suicidality or suicide ideation either with only symptoms of depression (Gijzen et al., 2021), or also with anxiety (Cai et al., 2023; Shen & Wang, 2023) or with a narrow range of non-symptom factors, such as variables associated with risky behaviour (Christian et al., 2021) or pain (Hinze et al. (2021). Fonseca-Pedrero et al. (2020) included a wide range of non-symptom risk factors but measured depression as a sum score. With reference to self-harm, Stone et al. (2017) used network analysis to investigate self-cutting risk amongst adolescent girls exposed to dating violence; and Hinze et al. (2021) investigated associations between self-harm and pain. More recent networks are including a broader range of non-symptom risk factors, for example, a

recent study by Zhong et al. (2023) included non-symptom risk factors related to school, bullying, social support, and loneliness, alongside depression symptoms.

1.8.5. Review of Network Studies Investigating the Association between Inflammation and Depression using Network Analysis

The network approach, with depression measured in terms of individual symptoms, has been used to examine relationships between inflammatory biomarkers and individual depression symptoms (Fried et al., 2020; Lee et al, 2023; Moriarity et al., 2021). However, all these studies measured appetite change (increased or decreased) as a compound symptom, and two also measured sleep as a compound symptom (Lee et al., 2023; Moriarity, et al., 2021). This could be obscuring important information related to the inflammation-depression relationship as the biological profiles of those with increased as opposed to decreased appetite, within the context of depression, has been found to differ (Lamers et al., 2013; Milaneschi et al., 2021; Milaneschi et al., 2020; Simmons et al., 2020).

1.9. Thesis Rationale

This thesis was motivated by two components: the need for more research investigating depression, suicidality, and potential depression biomarkers amongst Pacific young people and the opportunity provided by applying the network approach. There are few published studies that have investigated depression and suicidality amongst NZ Pacific adolescents and none that have measured depression in terms of individual symptoms or applied network analysis (see 1.4.2 Depression and suicidality amongst NZ Pacific people – Review of Literature). There are no studies examining the relationship between inflammation and depression amongst Pacific Young People in NZ. Therefore, this thesis helped fill those knowledge gaps with three original studies (details outlined below).

It also identified gaps within network literature. Most network studies investigating associations between individual depression symptoms with risk factors in adolescent depression have done so with a limited range of potential risk factors. Similarly, when investigating the relationship between depression symptoms with suicidality, previous network studies have controlled for a limited range of potential confounders (see 1.8.4 Review of Network Studies of Adolescent Depression, Suicidality and Self-harm). The current thesis included a wide range of multi-dimensional variables when conducting the network studies into risk factors for depression and the relationship between depression and suicidality. A few studies have investigated associations between inflammatory markers and depression symptoms using network analysis (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021), but they have measured the symptom relating to appetite change as composite, that is with increased and decreased changes combined (see 1.8.5 Review of Network Studies Investigating the Associations between Inflammation and

Depression using Network Analysis). The current thesis measured the symptom related to appetite as both composite, as per these earlier studies, and also as disaggregated into increased and decreased. For more detail about the thesis studies and chapters, see section below.

1.10. Thesis aims and research questions

1.10.1. Overall aim

- To apply the network approach to psychopathology, including measuring depression in terms of individual symptoms, to gain a deeper understanding of the relationships between depression symptoms with risk factors, with suicidality, and with inflammation amongst Pacific young people (adolescents and young adults) in NZ.

1.10.2. Research Questions

To achieve these aims it asked the following specific research questions:

1. What are the risk factors for depression amongst Pacific NZ adolescents? (This question was addressed in Chapter 3).
2. What is the impact of individual depression symptoms and self-harm on suicidality for Pacific NZ adolescents? (This question was addressed in Chapter 4).
3. Are certain depression dimensions, subtypes or individual depression symptoms more likely to be associated with inflammatory markers? (This question was addressed Chapter 5)
4. Is inflammation associated with depression in NZ Pacific young adults and what is the nature of the association? (This question was addressed in Chapter 6).

It also had four overarching goals, whose themes ran throughout the whole thesis. They were:

1. To appraise how measuring associations with depression in terms of individual symptoms provided valuable information that would be lost if depression was measured only in terms of a single sum score or even in terms of depression dimensions based on subscales of symptoms.
2. To detail how applying the network approach provides detailed and nuanced information that could then potentially be used to better inform treatment plans, therapies, and interventions.
3. To assess the extent to which direct and indirect associations, influential network nodes, possible feedback loops and symptom clusters, identified in the original studies (chapters 3, 4, and 6) were potentially shaped by cultural characteristics of the sample, and the implications for depression measurement, prevention, and treatment strategies.

4. To review the theoretical implications for depression measurement, based on the findings from all chapters, combined with published studies elsewhere.

1.11. Outline of thesis

1.11.1. Chapter 1 Depression and Suicidality amongst Pacific Young People and the Network Approach to Psychopathology

This chapter introduces the main elements that informed the thesis: depression and suicidality amongst Pacific young people in NZ and the network approach to psychopathology. It identifies the gaps in relevant literature and an outline of the thesis chapters and the contributions to knowledge.

1.11.2. Chapter 2 Methods and Measures

This chapter outlines the details of the participant samples and of the variables included the analyses; and the statistical methods used to estimate the networks, test for stability and robustness, and other network-based metrics and statistics used to reveal information on network structure.

1.11.3. Chapter 3 Risk Factors for Depression in Pacific NZ Adolescents?

This chapter investigated the associations between depression with a wide range of multi-dimensional potential risk factors, amongst Pacific NZ adolescents using network analysis. Depression was measured in two ways: 1) in terms of individual symptoms and 2) as a sum score of symptoms as a measure of depression severity. It addressed question 1 above.

1.11.4. Chapter 4 Understanding the Relationships between Depression Symptoms, Self-harm, and Suicidality in Pacific NZ Adolescents?

This chapter examined associations between individual depression symptoms with suicidality, pre and post adjusting for self-harm, and then separately after adjusting for a wide range of relevant psycho-social variables, amongst NZ Pacific adolescents using network analysis. It addressed question 2.

1.11.5. Chapter 5 Literature Review: Associations between Inflammatory Markers and Depression Dimensions, Subtypes, and Symptoms

This was a literature review of published research investigating associations between the three most studied inflammatory biomarkers (CRP, IL-6, and TNF-a) and depression dimensions, subtypes, and individual depression symptoms. The results of this literature review were used to inform the hypotheses in Chapter 6, and it addressed question 3.

1.11.6. Chapter 6 Associations between Inflammatory Markers and Depression amongst Pacific NZ Young Adults

This was a procedural replication of three previous network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021) and investigated links between inflammation and depression using network analysis, with depression measured in terms of the two main depression dimensions (psychological and somatic), and as individual symptoms. The symptoms related to appetite and sleep changes / disturbances were measured both as aggregated symptoms, which combined increased and decreased changes into compound symptoms, as per these other studies, and as disaggregated symptoms, measuring increased and decreased changes separately. It addressed question 4.

1.11.7. Chapter 7 Integrated Conclusion

This summarized the key findings, outlined how the thesis contributed to knowledge, its limitations and directions for future research.

1.12. Contribution to Knowledge

1.12.1. Contributions from Individual Studies

This thesis made a number of contributions to knowledge. The original studies described in chapters 3, 4, and 6 all broke new ground and contributed to knowledge in two main ways: 1) through the characteristics of the sample, and 2) through study design. These contributions are outlined in more detail below.

The study described in Chapter 3, has been published in the *Journal of Affective Disorders* (Gossage et al., 2022). It was the first time that associations between depression with potential risk factors had been investigated at the symptom-item level or using network analysis, amongst Pacific NZ adolescents, a population disproportionately at risk of significant depression symptoms. Secondly, it was the first network study of adolescent depression to investigate individual depression symptom-risk factor associations with such a wide, multi-dimensional set of risk factors. These risk factors covered almost every aspect of an adolescent's life, including socio-demographics, health, school, lifestyle, and a number of internalizing and externalizing behaviours, such as relationships (parents and friends), resilience, cultural identity, negative peer influence, substance use, impulsivity, and delinquency.

The study described in Chapter 4, has been published in the journal of *Suicidality and Life-Threatening Behavior* (Gossage et al., 2023). It represented the first time that associations between suicidality and depression had been investigated at the symptom item level or using network analysis for Pacific NZ adolescents, an under researched and at-risk population. Secondly, this was also the first study to use network analysis to investigate the influence of

self-harm and individual depression symptoms on adolescent suicidality, whilst adjusting for such a comprehensive set of possible risk factors. This reduces the risks that an association between two variables is spurious (Jones et al., 2017)

The study described in Chapter 6 is currently under review. It was the first study to investigate associations between inflammation and depression in Pacific people in NZ. As well as procedurally replicating three previous network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021), it also extended them. All these previous network studies measured the symptom construct for appetite disturbance as a compound symptom, whereby the nature of the disturbance (increased or decreased) was combined (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021)); and two also measured the symptom construct for sleep disturbance as compound (Lee et al., 2023; Moriarity et al., 2021). The study in Chapter 6, measured the symptoms related to appetite and sleep disturbance both as compound and disaggregated (which separated out the nature of the disturbance into increased and decreased). It also used an additional statistical methodology to estimate the networks to investigate how statistical methods may be influencing findings.

1.12.2. Overall Contributions to Knowledge

The thesis also made meta contributions to knowledge based on the cross-cutting themes present in all original studies. These contributions fell into three main areas: symptom-level measurement; the network approach, and cultural considerations; and in each area the implications for treatment and depression measurement were assessed. Overall, it also made a theoretical contribution based on the significance of the findings for depression measurement.

Prelude to Chapter 2

This chapter outlines the details of the participant samples, and the variables included the analyses; and the statistical methods used to estimate the networks, test for stability and robustness, and other network-based metrics and statistics used in the thesis.

Chapter 2. Methods and Measures

2.1. Participants

The data used in the studies described in Chapters 3, 4, and 6 were collected as part of the Pacific Islands Families (PIF) Study, an ongoing longitudinal study of a birth cohort of 1398 Pacific children born at a South Auckland hospital in NZ in the year 2000. Eligibility criteria for the PIF Study included having at least one parent who identified as being of a Pacific ethnicity and was a permanent resident of NZ. To date, data have been collected at regular intervals from 6 weeks onwards, with the data collected initially from one or more parents or guardians and then directly from the Pacific children (sometimes in conjunction with parental data) from nine years onwards (for further details on the PIF Study and characteristics of the cohort see Paterson et al., 2008). The data collected through the PIF Study is primarily self-reported and observational, and gathered by qualified assessors (for more detail on PIF Study data collection, see Sundborn et al., 2011). In some data collection waves, biological data has been taken, as in the study described in Chapter 6, investigating associations between depression and inflammatory biomarkers.

In the analysis in this thesis, Pacific New Zealanders are treated as one ethnic group, as sample sizes were not large enough to analyse them as separate ethnic groups, without substantial loss of power. Each Pacific island community does have its own cultural characteristics, but Pacific people share several cultural values, including spirituality, collectivism, importance of family, and behaving respectfully, particularly towards elders and people in positions of authority (Manuela & Sibley, 2013; Ministry of Pacific Peoples, 2022).

The data used in the studies in Chapters 3 and 4, were collected from 2017 to 2018, when the youth cohort turned 17. In the 17-year wave, 632 participants took part, but there were issues with missing data (see section 2.2 Missing Data and Participant Exclusion below for more details). The final analytic sample for the study in Chapter 3 comprised 561 participants. A table of participant demographics is shown below.

Table 1 Participant demographics for the study in Chapter 3

	Analytic sample n=561
	n (%)
Gender[a]	
Female	275 (49.0%)
Male	286 (51.0%)
Ethnicity	
Samoan	269 (48.0%)
Tongan	131 (23.4%)
Cook Islands Māori	82 (14.6%)
Other Pacific Island[b]	35 (6.2%)
Other[c]	44 (7.8%)
	Mean (SD)
Age	17 (0.35)

[a]The gender data used in this study were self-identified and collected in the 14-year wave as no gender data were collected in the 17-year wave. Participants were given the options of male, female or pass/don't know. The response of 'pass / don't know' was treated as missing data as cell counts for this response were very small

[b] This group was made up of those who identified as Tokelauan, Niuean, or Fijian.

[c]This group was made up of those who identified as Pākehā (European New Zealanders), Māori or multiple groups equally.

Due to further issues of missing data for the variables measuring suicidality, a further 11 participants had to be excluded for the study in Chapter 4 (see section 2.2 Missing Data and Participant Exclusion below)

Table 2 Participant demographics for the study in Chapter 4

	Analysis sample n=550
	n (%)
Gender[a]	
Female	270 (49.1%)
Male	280 (50.9%)
Ethnicity	
Samoan	263 (47.8%)
Tongan	129 (23.5%)
Cook Islands Māori	80 (14.5%)
Other Pacific Island[b]	35 (6.4%)
Other[c]	43 (7.8%)
	Mean (SD)
Age	17 (0.35)

[a]The gender data used in this study were self-identified and collected in the 14-year wave as no gender data were collected in the 17-year wave. Participants were given the options of male, female or pass/don't know. The response of 'pass / don't know' was treated as missing data as cell counts for this response were very small.

[b]This group was made up of those who identified as Tokelauan, Niuean, or Fijian.

[c]This group was made up of those who identified as Pākehā (European New Zealanders), Māori or multiple Pacific groups equally.

The data used in the study described in Chapter 6 were collected as part of a wider project investigating associations between depression with inflammatory biomarkers among the PIF Study cohort at the age of 20. There were interruptions in data collection due to COVID-19 alert level restrictions (for more information on COVID-19 alert levels and timelines see (Department of the Prime Minister and Cabinet, 2023). During alert levels other than level one, no data could be collected face to face and so no blood samples taken. Therefore, collecting face to face data had to stop when the alert levels rose above level one, and then resumed when alert levels fell again. A total of 377 participants completed questionnaires relating to psychological and covariate data and out of these 257 provided blood samples, with the data for 14 participants being excluded (see section 2.2.Missing Data and Participant Exclusion below). A further four were excluded as it was not possible to measure important blood biomarkers for this

group, although they did provide blood samples. This meant the final analytic sample comprised 239 participants. The characteristics of the sample are shown below.

Table 3 Participant demographics for the study in Chapter 6

	Analysis sample n=239
	n (%)
Gender[a]	
Female	143 (59.8%)
Male	96 (40.2%)
Ethnicity	
Samoan	109 (45.6%)
Tongan	55 (23.0%)
Cook Islands Māori	37 (15.5%)
Other Pacific Island[b]	15 (6.3%)
Other[c]	23 (9.6%)
	Mean (SD)
Age	19.85 (0.35)

[a]Participants were also given the option of 'Prefer not to say' and in the full sample (N=377), 3 chose this, but as the number was so small they were marked as missing.

[b]This group was made up of those who identified as Tokelauan, Niuean, or Fijian.

[c]This group was made up of those who identified as Pākehā (European New Zealanders), Māori or multiple groups equally.

2.2. Missing Data and Participant Exclusion

There were issues with missing data for the 17-year PIF Study data, that is data used for the studies in Chapter 3 and 4. The variable with the most missing data was one used to measure depression severity (included in the study in Chapter 3 only), with 48% of participants having one or more items missing on the depression inventory used, the Children's Depression Inventory Short Version (CDI:S) (Kovacs & Preiss, 1992), which has 10 items in total. This was

primarily for the depression symptom-item *Crying*[5]. Some of the other scale variables also had missing data over 10%. These were the variables created from summing items on the relevant psychometric inventories (see 2.3 Measures Chapters 3 and 4 for details of the variables and the psychometric inventories used). Problems with scale variables (which are made up of sum scores of symptoms) are common in psychological research, as even one item missing on the inventory means a scale score cannot be computed for that participant (Mazza et al., 2015). For the symptom-item *Crying*, 39% of participants had missing data. For the psychometric inventories measuring the quality of the relationships with father, mother, or friends, the missing data was as follows: for *Relationship with father,* 29% of participants had missing data for one item or more, for *Relationship with mother* this was 17%, and for *Relationship with friends*, 16%. Out of the other variables, that is the variables not made up of psychometric inventories, *Binge drinking* had the highest amount of missing data (21%). All other psychometric inventories and analysis variables had less than 10% missing data. The variable measuring *Suicidality* had 5% missing data and *Self-harm* had 6%.

Missing data analysis revealed that the missing data was not Missing Completely At Random (MCAR) (p-value based on Little's MCAR test < .0001) (Little, 1988), meaning that listwise deletion of participants with missing data could bias the analysis results (King et al., 1998) as well as leading to a substantial reduction in power. There was evidence, however, that the missing data was Missing at Random (MAR) (Rubin, 1976). Missing data analysis revealed that there were correlations between missing and observed data and there were also very high levels of correlations between the variables in the analysis, particularly between within-scale items on psychometric inventories. This made the data suitable for multiple imputation, which has shown to have high levels of accuracy for MAR data, including for the imputation of missing data in psychometric inventories (King et al., 1998; Xu et al., 2020).

As the data was mixed in type (numeric and categorical) and distributions of the numeric variables were skewed, data was imputed using a non-parametric, multiple imputation method, missForest (Stekhoven & Bühlmann, 2012), which has been shown to produce accurate results for MAR (and even Missing Not at Random (MNAR)), including for proportions of missing data up to 30% (Kokla et al., 2019). It (missForest) yields an out-of-the-bag (OOB) imputation error rate estimate, which is a validation technique used to measure the level of accuracy of the imputation using bootstrapped samples.

[5] In this thesis, there is a naming convention for the variables used in the analyses. When they are referred to, they are italicized with a capital letter to distinguish them from the general usage of similar terms.

To maintain data integrity and minimise any bias introduced by data imputation, all those participants missing data for more than 30% of the items on any of the psychometric inventories were removed from the analysis (see above, based on the work of Kokla et al., 2019); this amounted to 71 participants for the study in Chapter 3 and 82 for the study in Chapter 4, as there was additional missing data for the variables measuring self-harm and suicidality, which were not included in the study in Chapter 3. Data were imputed for the remaining missing data points. For the psychometric inventories, data were imputed at the item-level, not the scale level. Item-level imputation tends to result in higher precision than scale level imputation, as within scale item correlations tend to be high (Mazza et al., 2015). Scale variables, where relevant, were then created after imputation, by summing the item scores.

Accuracy of the imputation was assessed using normalized root mean squared error (NRMSE) for the continuous variables and proportion falsely classified (PFC) for the categorical variables. In both cases good performance is indicated by a value close to 0, and poor performance for values closer to 1 (Stekhoven & Bühlmann, 2012). The medians and distributions of the variables pre and post imputation were also compared using the Wilcoxon signed-rank test and the Kolmogorov-Smirnov test for the continuous variables and Pearson's chi-square test of homogeneity for the categorical variables.

Variable-wise error from the first run of data imputation showed that all variables were being estimated with a high or acceptable level of accuracy except for body mass index (BMI). Therefore, the missing values for *BMI* were imputed with the mean. Overall imputation error rates were 0.25 for PFC for the categorical variables, and 0.006 for NRMSE for the continuous variables, for both studies (Chapters 3 and 4)

There were much fewer problems with missing data for the year-20 data collection wave, the data used in the study in Chapter 6. The scale measuring alcohol consumption had the highest amount, but this was less than 2%. Data was imputed using the same methods as per the methods used for the studies in Chapters 3 and 4 (missForest) (Stekhoven & Bühlmann, 2012), and overall imputation error rates were 0.18 for PFC for the categorical variables and 0.05 for NRMSE for the continuous numeric variables. To prevent possible confounding, participants with CRP >10mg/L, which could signify high levels of acute inflammation, and with one or more self-reported chronic diseases, also associated with high levels of inflammation (cancer, diabetes, and heart disease), were removed from the analysis (n= 14), plus for 4 participants it was not possible to obtain key biomarker data for, although they did give blood samples.

2.3. Ethics Approval

The PIF Study has been guided by the Pacific People's Advisory Group and the collection and use of the data for the studies in Chapters 3, 4, and 6 approved by Auckland University of Technology Ethics Committee (AUTEC) (references 17/26 and 19/364 apply).

2.4. Measures Chapters 3 and 4

In Chapters 3 and 4, which used data collected during the year-17 data collection wave, a wide range of socio-demographic, psychosocial, and behavioural data were included, alongside depression data. These variables are described below.

2.4.1. Depression Measurement

In Chapter 3, depression was measured in two ways, as a sum score of depression symptoms and in terms of individual depression symptoms. In Chapter 4, depression was measured only in terms of individual symptoms. The depression inventory used in both studies was the CDI:S (Kovacs & Preiss, 1992). The CDI:S is a 10-item, self-rated symptom scale, suitable for youths aged 7 to 17 years and has been widely used in research and clinical practice. It has been shown to be a reliable measure of depressive symptoms (Klein, Dougherty, & Olino, 2005). In this study, items on the CDI:S were scored 1 to 3 (often they are scored 0 to 2), and after reverse scoring relevant items, higher symptom scores corresponded to higher symptom severity, with a range from 10 to 30. The symptom scores were then summed to create a single scale to measure *Depression severity*, with higher scores corresponding to higher depression severity.

2.4.2. Socio-demographic Variables

The socio-demographic variables of gender, ethnicity, and socio-economic deprivation were included in the study. The level of socio-economic deprivation was assessed with a self-reported measure of food security, *Money for food*. To check data reliability, the data from the *Money for food* variable were cross referenced with data from the NZ index of socioeconomic deprivation for individuals (NZiDep), collected at the 14-year wave from the primary carers, predominantly mothers, of the participants. The two measures were found to be significantly correlated (r_s=0.17 $p<0.001$)[6], providing confidence in the self-reported data from the youth participants.

[6] The two measures of socio-economic deprivation were not exactly the same, one measured the extent of food insecurity and the other the number of deprivations experienced. Therefore, the correlation coefficient between the two would not be expected to be very high. The aim was to test whether they were significantly correlated to provide confidence in the *Money for food* deprivation measure, self-reported by the adolescents.

Data were collected when all participants were very close in age (M = 17.0, SD = 0.35), therefore age was not included as a variable.

2.4.3. Psychosocial and Behavioural Variables

The following variables were measured using psychometric inventories and scales*: Depression severity, Relationship with mother, Relationship with father, Relationship with friends, Impulsivity, Delinquency, Negative peer influence, Gang involvement, Resilience*, and Pacific identity, which was measured with the following subscales *Cultural Efficacy* (CE), *Group Membership Evaluation* (GME), *Religious Centrality and Embeddedness* (RCE), and *Pacific Connectedness and Belonging* (PCB). For more information about these inventories and scales see Appendix A, Table A-2. Confirmatory Factor Analysis (CFA) was performed on the items making up each inventory, using R package Lavaan (Rosseel, 2012), to check whether they supported first a single factor solution, and if not then whether they could be used in terms of subscales (See Table 4 below for the results of the CFA for the sample in Chapter 3; the CFA results for Chapter 4 are in Appendix B, and are almost identical). Single variables were then created by summing the scores of the inventory items, after any necessary reverse coding. The following indices of model fit were used with the shown thresholds: the comparative fit index (CFI) (CFI >= 0.95 a good fit, and between=0.90 and 0.95 an acceptable fit), Tucker Lewis index (TLI) (TLI >=0.95 a good fit, between 0.90 and 0.95 an acceptable fit), root mean squared error approximation (RMSEA) (RMSEA less than 0.05 a good fit, between 0.05 and 0.08 moderate, and over 0.1 a poor fit), and standardized root mean square residual (SRMR) (SRMR less than 0.08 considered a good or acceptable fit (Kline, 2005) (Browne & Cudeck, 1993; Leandre R. Fabrigar et al., 1999; L.-t. Hu & P. M. Bentler, 1999; R. Schumacker & R. Lomax, 2016). To account for the ordinal nature of the data, estimators were calculated using diagonal weighted least squares with robust standard errors, available through the Lavaan package (Rosseel, 2012).

Table 4 Results of the confirmatory factor analysis of psychometric inventories used in Chapters 3 and 4

Fit measures / Inventories	CFI	TLI	SRMR	RMSEA	df[c]
Relationship with father[a]	0.94	0.94	0.07	0.10[a]	275
Relationship with mother	0.90	0.90	0.08	0.10[a]	275
Relationship with friend	0.90	0.89	0.08	0.09	275
Depression Severity	0.98	0.97	0.05	0.04	35
Impulsivity	0.99	0.98	0.02	0.06	2
Delinquency	0.99	0.98	0.05	0.05	20
Resilience	1.00	0.99	0.02	0.05	2
Pacific Identity as sub scales (CE, GME, PCB, and RCE)	0.95	0.94	0.07	0.07	183

	Cronbach's alpha				
Gang Involvement[b]	0.94				
Negative peer influence[b]	0.83				

[a]Relationship with father and *Relationship with mother* were at the upper end of the range for RMSEA in terms of acceptable model fit (0.1), but as all the other chosen CFA measures (CFI, TLI, SRMR, RMSEA) were within acceptable range there were both fitted as one scale (Browne & Cudeck, 1992; Leandre R Fabrigar et al., 1999; L. t. Hu & P. M. Bentler, 1999; E. Schumacker & G. Lomax, 2016). All other inventories showed good or moderate fit in terms of the chosen CFA measures (Browne & Cudeck, 1992; Leandre R Fabrigar et al., 1999; L. t. Hu & P. M. Bentler, 1999; E. Schumacker & G. Lomax, 2016).

[b]The CFA models for Gang involvement and Negative peer influence were over saturated (df=0) as the inventories consisted of only three items. Therefore, Cronbach's alpha was used instead.

[c]df = degrees of freedom.

Other variables included in the analyses in Chapters 3 and 4 (that were not created from psychometric inventories) were *Church attendance, Ever had sex, Hours online, Online bullying – victim, Online bullying – perpetrator, Attend school*, School connectedness (*Part of school*), rapport with teachers (*Get along with teachers*), *Binge drinking*, *Smoke cigarettes* (*Smok*e), *Smoke marijuana, Take legal highs*, (for example, party pills), *BMI*, self-rated health (*Health*), *Energy levels*, and *Self-assessed weight*. Weight and height measurements, used to calculate BMI, were taken by the study assessors, otherwise all data were self-reported.

2.4.4. Standardisation of Measures Chapters 3 and 4

The inventory measuring depression symptoms in both Chapters 3 and 4 was the CDI:S (Kovacs & Preiss, 1992), but the variable labels used for some of the symptoms across these chapters varied. In Chapter 3, they were labelled very literally, to give full descriptive power to the associations with risk factors. In Chapter 4, the results were being compared with other studies that had used the same or similar inventories. Therefore, the symptoms were labelled based on the construct they were measuring to make comparisons easier. The Table below outlines each symptom as it was labelled in Chapter 3 and its equivalent label in Chapter 4.

Table 5 Symptom Labels in Chapters 3 and 4

Symptom labels in Chapter 3	Equivalent symptom labels in Chapter 4
Alone	*Loneliness*
Sad	*Sadness*
Cry	*Crying*
Looks	*Negativity towards looks*
Bothered	*Irritability*
Not enough friends	*Lack of friendship*
Not work out	*Pessimism*
Does things wrong	*Self-criticism*
Self-hatred	*Self-hatred*
Love	*Feels unloved*

2.5. Measures Chapter 6

Chapter 6 used data collected during year-20 data collection wave, and included depression, biomarker, and covariate data. The data used to calculate BMI also included data collected during the year-17 data collection wave. See below for details.

2.5.1. Depression

Depression was measured in terms of two depression dimensions, psychological and somatic, and by individual symptoms. Psychological depression symptoms were measured using the Beck Depression Inventory (BDI) - Fast Screen (BDI-FS) (Beck et al., 2000), a short version of the 21 item BDI-II (Beck, 1996), which omits somatic symptoms and has shown good reliability in general populations (Kliem et al., 2014). Somatic depression symptoms were measured using BDI-II items 15–21 as has been used elsewhere (Thombs et al., 2010). For all depression symptoms, except those relating to sleep and appetite, possible responses ranged from 0-3 on a Likert scale, with 0 representing an absence of that symptom, and 1 to 3 its presence, with higher scores denoting higher symptom severity. For the sleep and appetite symptoms, there were 7 possible options (coded 0, 1a, 1b, 2a, 2b, 3a, and 3b), to enable both increases and

decreases in sleep and appetite to be captured. No disturbances of any kind for sleep and appetite were represented by 0, and then there were three options of increasing severity each for both increased and decreased sleep and appetite.

To assess the severity of psychological and somatic dimensions of depression, two subscales were created. Psychological depression was assessed by summing the 7 items on the BDI-FS (Beck et al., 2000). Somatic depression was assessed by summing the items 15-21 of the BDI-II (Beck, 1996). Higher scores denoted higher severity of that depression dimension. When summing symptom scores to create the depression subscales, the items related to sleep and appetite were recoded into 4 levels of increasing severity (0,1,2, and 3), irrespective of the nature of the disturbance, and given a score of 0 to 3 as per the other symptoms. Cronbach's alpha was used to check the internal consistency of summing items to make the two scales (Cronbach, 1951), using R package Psych (Revelle & Revelle, 2015). Results showed good internal consistency for both the psychological and somatic depression subscales, with alphas of .84 and .83, respectively.

For the analyses of individual depression symptom items, all symptoms, except those related to sleep and appetite, were dichotomized into 1/0= presence/absence of the symptom, due to small cell counts in the levels of certain symptoms and the skewed distributions of the symptoms. All non-zero responses were regarded as presence of a symptom. As the two BDI-II items relating to sleep and appetite included options for both increased and decreased sleep or appetite, the sleep and appetite symptoms were composed in three different ways: as binary composite symptoms (for example, no appetite disturbance of any kind (coded 0) versus appetite disturbance of any kind (increased or decreased) (coded 1)); as binary disaggregated symptoms (for example, no increased appetite (coded 0) versus increased appetite (coded 1)), and as 3-level categorical variables with each level corresponding to the nature of the disturbance (1 = none (no disturbance of any kind), 2 = less (that is disturbances leading to decreased sleep, or decreased appetite in case of that symptom), and 3 = more (that is disturbances leading to increased sleep, or increased appetite for that symptom).

2.5.2. Inflammatory Markers

The data for the biomarkers being investigated (*CRP, IL-6*, and *TNF-a*), were collected through serum blood samples. Special tubes without anticoagulant or Serum Separator Tubes (SST, BD Vacutainer®) were used to collect blood samples (one 13 x 75 mm x 8.5 mL tube per fasting participant) and inverted 5 to 10 times to activate clotting before leaving the tubes undisturbed in an upright position at room temperature for 30 minutes. Tubes showing signs of haemolysis were discarded as haemoglobin may interfere with some tests. Tubes were kept at low temperature (+4°C) and immediately transported to the Auckland University of Technology (AUT) Roche Diagnostics Laboratory where they were centrifuged to get the serum samples. As

specimens were processed in batches, serum samples were stored at -20°C to ensure the stability of the biomarkers over time.

2.5.3. Covariates

Covariates were chosen to align with the three previous studies, that the study in Chapter 6 was replicating (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021), which in turn was based on previous research that aimed to minimise confounding (e.g. Duivis et al., 2013). Age was excluded in the study in Chapter 6, as there was not enough variability as all participants were very close in age (Mean=19.85 (SD=0.35)). Covariates were *Gender* (0=male, 1=female)[7], *Smoking* (1=never, 2=past, 3=current), *Exercise* (0=no, 1=yes), *BMI*, and Alcohol consumption (*Alcohol*) (assessed with the Alcohol Use Disorders Test of Consumption (AUDIT-C)) (Bush et al., 1998).

2.5.3.1. Exercise

Exercise was modelled as a binary variable and was created from text data. Participants were not asked specifically about the amount of exercise that they did, but they were asked about their favourite recreational activities. All those who chose at least one physically active and sport-related hobby were coded as 1, others as 0.

2.5.3.2. Alcohol

Alcohol consumption was modelled as numeric continuous and was assessed with three questions on the Alcohol Use Disorders Identification Test (AUDIT), related specifically to alcohol consumption (AUDIT-C) (Bush et al., 1998):1) how often do you have a drink containing alcohol? (never to more than 3x a week); 2) how many drinks containing alcohol do you have on a typical day when you are drinking? (1 or 2 to 10 or more); 3) how often do you have six or more drinks on one occasion? (never to daily or almost daily). The answers were summed to create a score.

2.5.3.3. BMI

BMI, (calculated as weight in kilograms divided by height in metres squared (kg/m^2)), was composed of both self-reported data (for weight and height) collected during the year-20 data collection wave, supplemented with weight and height measurements collected accurately by study assessors during the year-17 data collection wave, as some of the self-reported BMI data collected in the year-20 wave was inaccurate. When it was necessary to use year-17 BMI data, a

[7] Participants were given the options of male, female and prefer not to say. Three participants from the full sample marked 'prefer not to say' but as this number was too small to analyse separately, they had to marked as missing data.

growth factor was added to the year-17 BMI data, based on BMI growth charts from the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention, 2022). Formulation of the *BMI* variable involved four stages:

- Stage one - a BMI variable was created, based on year- 17 data, with a BMI growth multiple added based on CDC BMI growth charts for males and females. For example, at year 17, mean BMI for males in the sample used was 31 kg/m^2. This mean was in the 97^{th} quartile of the CDC BMI growth chart, and based on these chart approximations, would grow by 8% by age 20.
- Stage two - the year-20 data was checked for obvious discrepancies, for example, all those who self-reported height at 20 as less than that measured at age 17 were coded to missing. Also, all self-reported BMIs at year-20 that were more than 3 SDs from the predicted BMIs based on year-17 data were also coded as missing.

- Stage 3 – All the missing BMI data was inputted, where possible, with the predicted BMIs based on year-17 data plus growth factors for males and females, and if this was not available then was left as missing and then inputted using missForest alongside other missing data. Overall, five data points could not be replaced with the created BMI variable and had to be inputted with missForest.
- Stage 4 – the accuracy of the predicted BMI was checked against actual, plausible BMIs, to verify reliability of using this method.

2.5.3.4. COVID 19

The effect of COVID-19 alert level restrictions was not controlled for due to the difficulty in accurately and reliably assessing the impact of COVID-19 on the data. A small number of participants completed questionnaires and had bloods taken prior to any COVID-19 alert levels (n=20), but after the reporting of COVID-19 cases in NZ, in the run-up to the first lockdown. The rest of the data were collected between lockdowns, when COVID-19 alert levels permitted this. However, as all data was collected during the period of high COVID-19 media coverage and given that the sample was homogeneous, with regard to age, Pacific ethnicity, and location (all lived in Auckland), it was considered reasonable to assume that all participants were similarly affected by the COVID-19 events.

2.6. Data Analysis

Statistical analysis was completed using statistical software R (R Core Team, 2020) augmented by various R packages. As all the numeric variables had skewed distributions, they were normalized using the non-paranormal transformation (Liu et al., 2009)

2.6.1. Network Estimation

2.6.1.1. Mixed Graphical Models

The data was modelled using undirected mixed graphical models (MGMs). MGMs are a sub-genre of undirected graphical models, which are families of probability distributions that satisfy the property for pairwise Markov random fields. A Markov random field is depicted in the form of a network graph, where nodes represent components, and the edges represent conditional dependencies between nodes (Pieczynski & Tebbache, 2000). The pairwise Markov property states that if two nodes are unconnected (there is no edge between them), they are conditionally independent, given all other variables in the network graph (Pieczynski & Tebbache, 2000). If two nodes are connected, we say they are dependent conditional on all other nodes in the network (for more information on conditional independence see Dawid, 1979). The mgm used to analyse the data in this study is one that permits the modelling of variables of different types (binary, categorical, continuous), and it is estimated using the mgm package in R (Haslbeck & Waldorp, 2020).

2.6.1.2. Estimation of Edge Weights

The mgm-package uses neighbourhood nodewise regression to estimate parameters, which are then combined into an edge weight (w), an absolute value that quantifies the strength of an association (Haslbeck & Waldorp, 2020). This method uses nodewise regression to estimate edge weights (Meinshausen & Bühlmann, 2006). With this method, each node is regressed on all other nodes in the network using the appropriate general linear model, for example, linear regression for continuous dependent node, logistic regression for binary dependent node, and multinomial regression for categorical dependent nodes with more than two levels. If the pairwise interaction involves continuous variables only, then only one parameter is calculated, and its absolute value is the edge weight. For categorical variables, the mean of the absolute value of all parameter estimates is combined into an edge weight. For pairwise interactions involving categorical variables, this means two edge-weights are estimated: one regressing node S on node R and another regressing node R on node S. These two edge-weights are combined into a single edge-weight using the AND or the OR rule. For pairwise interactions under the AND rule, the mean of the two edge-weights is used to calculate the final edge weight, provided both edge-weights are non-zero, otherwise the edge-weight is set to zero. For pairwise interactions under the OR rule, the arithmetic mean of two edge-weights is taken, even if one of them is zero (Haslbeck & Waldorp, 2020). The AND rule has higher specificity and lower sensitivity than the OR rule, which has the reverse (Haslbeck & Waldorp, 2020). For all original studies in this thesis the more conservative AND rule was used.

2.6.1.3. Regularized Networks

Network estimation usually involves a high number of parameters to be estimated and so carries a risk of false positives (also referred to as spurious edges). To reduce the risk of spurious edges, the most common methods to estimate psychological networks usually involve regularization with least absolute shrinkage and selection operator (LASSO) (Tibshirani, 1996; Epskamp & Fried, 2018). LASSO shrinks small edge weights to zero via a penalty parameter lambda (for more on LASSO regularization see (Tibshirani, 1996)).

Using the mgm package in R, there are two options which can be used to calculate lambda: K-fold cross validation (CV) or Extended Bayesian Information Criterion (EBIC) (Haslbeck & Waldorp, 2020). Using k-fold CV, the data is split into equal parts or folds with each part serving as the test set for the model built in the training set. For example, in 10-fold cross-validation, the data is split into 10 equal parts with the model built in 90% of the data and then tested in the remaining 10% of the data. Each part serves as the test set and the mean squared error is averaged across all the folds. Lambda is selected based on the value that minimises mean squared error (MSE) (Hastie et al., 2009). A higher value for k reduces bias but increases variance and vice versa. For this thesis, k=10 was chosen as this has shown to provide a good balance between bias and variance (Berrar, 2019).

Under EBIC, lambda is selected by minimising the negative log likelihood function plus an additional term, which includes a hyperparameter gamma (for more on EBIC see (Chen & Chen, 2008). Gamma can be set at any value from 0 to 1 and when it is zero, EBIC is equivalent to Bayesian Information Criterion (BIC) (for more on BIC see (Schwarz, 1978)).

Generally, selecting lambda with CV leads to models with lower specificity and higher sensitivity (Wysocki & Rhemtulla, 2021) and lambda selected with EBIC tends to favour sparse graphs (Foygel & Drton, 2010), although the extent of this depends on the value of gamma (the hyperparameter) chosen. In this thesis, both methods were used to calculate lambda, CV and EBIC. See below.

2.6.1.4. Penalty Parameters used in this Thesis

In Chapter 3, EBIC was used to calculate lambda, with the hyperparameter set at 0.25 and 0.5, as the aim of this study was to identify the strongest associations between a wide variety of potential risk factors and depression symptoms, and this was aided by penalising complexity. In Chapter 4, the aim was to detect associations between suicidality with depression symptoms, with one network model adjusting for a large number of potential confounders. Therefore, CV was used to calculate lambda, to ensure important associations between depression symptoms with suicidality were not shrunk to zero due the large number of variables adjusted for. In Chapter 6, lambda was calculated using both CV and EBIC, but with the hyperparameter set to

zero in EBIC, so the equivalent of BIC. The gamma parameter in the model was set at 0 for the main network models because associations between variables from different domains (e.g. between depression symptoms (psychological domain) and inflammatory markers (biological domain)) are likely to be much weaker than associations between variables from the same domain (e.g. symptom-symptom associations) and so are more likely to be shrunk to zero by the LASSO (Epskamp & Fried, 2018). The study in Chapter 6 was a procedural replication of three other network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021) and setting gamma to zero was also in line with methods used by the two of three studies the study in Chapter 6 was procedurally replicating (Fried et al., 2020; Moriarity et al., 2021). The study in Chapter 6 also fitted networks without regularization, in line with the methodology used in all of the three studies that the study in Chapter 6 was replicating (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021). The study described in Chapter 6 additionally fitted networks with regularization using CV to assess how different methods for calculating the penalty parameter affected findings.

2.6.1.5. Network Visualisation

Graphical representations of the network models were performed via the integration of the mgm package with qgraph package (Epskamp et al., 2012). The Fruchterman-Reingold algorithm was used in this procedure to place nodes with stronger connections closer together. In the network graphs, wider and more colour-saturated edges depicted stronger associations and the colour the direction of the association between two nodes: blue represented a positive association, red a negative association, and grey meant the direction could not be obtained from the network graph (as one of the variables was a categorical variable with more than 2 levels), but could be identified from post hoc investigations using methods available in the mgm package. The predictability of each node was shown by the shaded pie segment. This was light blue for numeric variables and represented R-squared; and for the categorical variables the yellow part of the segment represented the predictability of the intercept model, the red part the additional predictability by neighbouring nodes, and the sum of both segments the predictability of the whole model.

2.6.1.6. Network Node Influence

Two methods were used to assess potential node influence: 1) nodewise predictability (Haslbeck & Waldorp, 2018); and 2) node centrality (Barrat et al., 2004; Freeman, 2002; Opsahl, 2010). (Haslbeck & Waldorp, 2018).

Predictability, which is the extent to which a node can be determined by other nodes in the network, was quantified using proportion of variance explained for numeric nodes (similar to R-squared) and normalized accuracy for the categorical nodes. Normalized accuracy calculates the overall accuracy of the model, including the intercept model, and the additional accuracy achieved by the model over and above the intercept only model (Haslbeck & Waldorp, 2018).

The centrality measures used were Strength, Degree, Betweenness, and Closeness (Barrat et al., 2004; Freeman, 2002; Opsahl, 2010). Centrality metrics quantify aspects of node connectivity within the network. Strength is calculated by summing the absolute value of edge weights connected to a node; Degree by summing the number of edges connected to a node; Betweenness by counting the number of times a node lies on the shortest path between two other nodes; and Closeness by the average distance from a node to other nodes (Costantini et al., 2015; Opsahl, 2010). It has been argued that Betweenness and Closeness centralities come with assumptions that may not hold in psychological networks, as they were developed essentially for social networks, so need to be interpreted with caution (Bringmann et al., 2019). Centrality measures are only interpretable if the networks reach a threshold of stability (see 2.6.1.7 Network Stability below).

2.6.1.7. Network Edge Reliability

Pairwise edge reliability was assessed by calculating edge probability inclusion rates (PIRs) derived from non-parametric bootstrap resamples using the resample function in mgm package in R (Haslbeck & Waldorp, 2020) and bootnet package in R (Epskamp et al., 2018), as used elsewhere (Fried et al., 2020; Moriarity et al., 2021). The PIR represents the percentage of bootstrap resamples where the edge was non-zero. A high PIR of a given edge across bootstrap samples provides evidence for the presence of the edge in the true model. It is particularly important to assess PIR rates with networks regularized with CV and for unregularized networks, as spurious edges are more likely with these methods.

2.6.1.8. Network Stability

The stability of the centrality indices was assessed using the centrality stability (CS) coefficient, using bootnet in R (Epskamp et al., 2018). This calculates the maximum proportion of cases that can be dropped from the dataset whilst still maintaining a correlation of at least 0.70 between the original network and the data with the cases removed, with 95% probability. CS-coefficients should ideally be 0.5 or more and should not be below 0.25 (Epskamp et al., 2018).

2.6.1.9. Identifying Redundant Nodes

Redundant nodes, nodes that are too topologically similar, can cause problems for network analysis, as they may be measuring the same construct. Therefore, the goldbricker function in R package NetworkTools (Jones, 2020) was used to identify redundant nodes, in Chapters 3 and 4. Networks, however, were fitted with and without the nodes identified as redundant by goldbricker to assess how it was affecting findings. In Chapter 6, goldbricker was not used as the aims of the study required that all nodes be included.

Goldbricker compares the correlations in a network to identify those nodes which may be measuring the same construct. The goldbricker package works on the principal that if two nodes

are measuring the same construct, then the association between these two nodes and all other nodes in the network would be highly similar. Goldbricker calculates the proportion of correlations which are significantly different for each pair of nodes, based on a threshold. All pairs of nodes which fall below this threshold are defined as “bad pairs” and one should be dropped or the pairs combined into one construct, provided they also meet a minimum zero-order correlation threshold (Jones, 2020). In this study, the dropping method was used, with the default threshold setting of 0.25 and minimum correlation of 0.5; that is if a pair of nodes had a proportion of significantly different correlations less than 0.25, then they were classed as “bad pairs”, provided they had a minimum zero-order correlation between them of 0.5.

Chapter 3 Prelude

This chapter investigated the associations between depression with a wide range of multi-dimensional potential risk factors, amongst Pacific NZ adolescents using network analysis. Depression was measured in two ways: 1) in terms of individual symptoms and 2) as a sum score of symptoms as a gauge of depression severity. It has been published in the Journal of Affective Disorders (Gossage et al., 2022).

Chapter 3. Risk factors for Depression in Pacific NZ Adolescents

3.1. Introduction

Adolescent depression is a serious and growing health issue and is one of the leading causes of illness and disability amongst adolescents (WHO, 2020). As with many countries worldwide, the prevalence of youth depression in NZ is increasing. Between 2012 and 2019, rates of depressive symptoms amongst NZ adolescents rose from 13% to 23% (Fleming et al., 2020). A recent report on youth mental health in NZ found it was declining and its impact on certain groups, including female, Māori and Pacific youth was disproportionate. The report called for a greater sense of urgency to deal with this mental health crisis (Menzies, Gluckman, & Poulton, 2020). Around 25% of Pacific adolescents in NZ report significant depressive symptoms compared with 20% for their Pākehā[8] (NZ European) peers and these inequities are primarily gender driven. Around 33% of Pacific female adolescents reported significant depressive symptoms, compared with 15% for Pacific male adolescents (Fleming et al., 2020). Pacific youth are also more likely to attempt suicide, 12% compared to 3% of Pākehā and other European youth[9] (Fleming et al., 2020). Nevertheless, despite evidence of higher prevalence of depression, very few adolescent and youth studies have been conducted on Pacific wellbeing (Tucker-Masters & Dr Tiatia-Seath, 2017).

The Pacific population in NZ comprises those whose heritage traces back to various Pacific islands, with the largest groups from Samoa (48%), Tonga (22%), and the Cook Islands (21%), but also including Fiji, Niue, and Tokelau. This population is highly urbanized, with around two thirds living in the Auckland region, and young, with a median age of 23 years compared with 38 years for NZ as a whole (Statistics NZ, 2018). Pacific people in NZ are also more religious than New Zealanders generally, with only 23% of Pacific New Zealanders stating they have no religion, compared to the national average of 48%. Pacific people in NZ suffer disproportionate socioeconomic deprivation compared to New Zealanders generally; for example, they are disproportionately located in the Auckland's poorest suburbs (Ministry of Health, 2021b) and a recent survey found that 37% of Pacific children live in severe to moderate food insecure households compared to 19% for NZ children overall (Ministry of Health, 2019).

Heterogeneity of cause and symptom presentation makes full understanding of depression in adults and younger people challenging (Mullarkey, Marchetti, & Beevers, 2019; Thapar,

[8] Pākehā is a Māori language term used to describe the inhabitants of NZ with European heritage.

[9] Māori are also disproportionately likely to report significant depressive symptoms and attempt suicide and whilst this is also of concern Māori are not the focus of the present research.

Collishaw, Pine, & Thapar, 2012). That is, depression is multifactorial and contextually driven and thought to result from complex interactions between several risk factors and causal pathways (Maughan, Collishaw, & Stringaris, 2013). Network analysis is a visualization tool suitable for displaying such complex relationships (Haslbeck & Waldorp, 2018; McNally, 2016; Van Borkulo et al., 2014; Van Borkulo. et al., 2017). Following pioneering work by researchers in this field (Borsboom, 2008; Borsboom & Cramer, 2013; Boschloo, Schoevers, van Borkulo, Borsboom, & Oldehinkel, 2016; Fried & Nesse, 2015a; Fried et al., 2017; McNally, 2016) psychological network analysis is being increasingly used to investigate depression at the symptom level rather than measuring depression as a single item construct, calculated by summing the symptom scores. According to this network model of psychopathology, depression is inadequately described by summing symptom scores to create a single latent construct, rather the symptoms are the disorder (Borsboom, 2008; Borsboom & Cramer, 2013; Fried & Nesse, 2015a; Fried & Nesse, 2015b; Fried et al., 2017). Depression symptom networks provide valuable information about symptom importance that could be used to guide the design of symptom specific interventions and therapies (Fried & Nesse, 2015b; Fried et al., 2017; McNally, 2016).

Several previous studies have modelled preadolescent or adolescent depression data using network analysis (Bodner et al., 2018; Boschloo et al., 2016; Fritz et al., 2018; Hukkelberg & Ogden, 2018; Jones et al., 2018; Kim et al., 2021; McElroy et al., 2018; Mullarkey et al., 2019; Schweren et al., 2018), but none, to the authors' knowledge, with Pacific adolescents. Given that network analyses are sensitive to culturally specific results (Kim et al., 2021; Wasil et al., 2020), the applicability of network results across cultures and ethnicities cannot be assumed. Thus, if network analysis is to fulfil its potential as an aid to clinical decision making, more culturally and ethnically specific network analyses are needed. The veracity of this technique is also influenced by the number and quality of the variables in the analysis and rich data are likely to provide more informative results.

To address this gap in network literature, this study used network analysis to model the cross-sectional associations between depression and a particularly rich multidimensional set of variables in a sample of Pacific adolescents in NZ, including variables covering socio-demographics, health, school, lifestyle, and a number of internalizing and externalizing behaviours, such as relationships (parents and friends), resilience, Pacific cultural identity, negative peer influence, substance use, impulsivity, and delinquency. Past research has shown that these variables could have an impact on depression (Barcaccia et al., 2020; Boers et al., 2019; Bukowski et al., 1996; Carbonell et al., 2002; Carlson & Cantwell, 1980; Clayborne et al., 2019; Lundervold et al., 2013; Paterson et al., 2014; Piko & Pinczés, 2014; Remes et al., 2019; Tang et al., 2019). To the authors' knowledge, this is also the first study to investigate such a

wide range of possible risk factors for depression severity and depression symptoms amongst adolescents, using network analysis.

This current research builds on important work, conducted by the Pacific Islands Families (PIF) Study team, that investigated risk and protective factors for child and adolescent depression up to the age of 14 amongst Pacific youth (Paterson et al., 2014; Paterson, Tautolo, Iusitini, & Sisk, 2018).

3.2. Methods

3.2.1. Source of Data and Participants

The data used in this study were collected as part of the PIF Study, an ongoing longitudinal study of a birth cohort of 1398 Pacific children born at a South Auckland hospital in NZ in the year 2000. Eligibility criteria for the PIF Study included having at least one parent who identified as being of a Pacific ethnicity and was a permanent resident of NZ. The PIF study has been guided by the Pacific People's Advisory Group and approved by Auckland University of Technology Ethics Committee (AUTEC) (references 17/26 and 19/364 apply). To date, data have been collected at regular intervals from 6 weeks to 20 years of age. The current cross-sectional analysis used data collected from 2017 to 2018, when the youth cohort turned 17. In the 17-year wave, 632 participants took part, but there were issues with missing data. Therefore, the final analytic sample included 561 participants (see Results section for more details of participant removal and missing data strategies). Further details on the PIF Study and characteristics of the cohort are available elsewhere (Paterson et al., 2008).

3.2.2. Variables Included in the Analysis

Depression was measured in two ways, as a single latent construct and in terms of individual depression symptoms, using the shorter version of the Children's Depression Inventory (CDI:S) (Kovacs & Preiss, 1992). The CDI:S is a 10-item, self-rated symptom scale, suitable for youths aged 7 to 17 years and has been widely used in research and clinical practice. It has been shown to be a reliable measure of depressive symptoms (Klein, Dougherty, & Olino, 2005). In this study, items on the CDI:S were scored 1 to 3, and after reverse scoring relevant items, higher symptom scores corresponded to higher symptom severity. The symptom scores were then summed to create a single scale to measure *Depression severity*, with higher scores corresponding to higher depression severity.

The socio-demographic variables of *Gender*, *Ethnicity*, and socio-economic deprivation were included in the study. The level of socio-economic deprivation was assessed with a self-reported measure of food security, *Money for food*. To check data reliability, the data from the *Money for food* variable were cross referenced with data from the NZ index of socioeconomic deprivation

for individuals (NZiDep), collected at the 14-year wave from the primary carers, predominantly mothers, of the participants. The two measures were found to be significantly correlated (r_s=0.17 p<0.001)[10], providing confidence in the self-reported data from the youth participants. Data were collected when all participants were very close in age (M = 17.0, SD = 0.35), therefore age was not included as a variable.

The following variables were measured using psychometric inventories: *Depression severity, Relationship with mother, Relationship with father, Relationship with friends, Impulsivity, Delinquency, Negative peer influence, Gang involvement, Resilience*, and Pacific identity, which was measured with the following subscales Cultural Efficacy (*CE*), Group Membership Evaluation (*GME*), Religious Centrality and Embeddedness (*RCE*), and Pacific Connectedness and Belonging (*PCB*). Confirmatory Factor Analysis (*CFA*) was performed on the items making up each inventory, using R package Lavaan (Rosseel, 2012), to check whether they supported first a single factor solution, and if not then whether they could be used in terms of subscales. Single variables were then created by summing the scores of the inventory items, after any necessary reverse coding. See Chapter 2 Methods and Measures, Table 4 for the results of the CFA.

Other variables used in the analysis included *Church attendance, Binge drinking, Smoke cigarettes, Smoke marijuana, Take legal highs, (*for example, party pills*), Ever had sex, Hours online, Online bullying - victim, Online bullying - perpetrator, Attend school, Part of school*[4]*, Get along with teachers*[11]*,* body mass index *(BMI), Health, Energy levels*, and *Self-assessed weight*. Weight and height measurements, used to calculate *BMI*, were taken by the study assessors, otherwise all data were self-reported. See Table 6 below for the summary characteristics of the both the full year-17 sample (N=632) and the analytic sample (n=561) and Appendix A Tables A-1 and A-2 for a more detailed description of all the analysis variables, their distribution, and the psychometric inventories used.

3.2.3. Statistical Analysis

Statistical analysis was completed using statistical software R (R Core Team, 2020) augmented by various R packages. All continuous numeric variables showed skewed distributions and so

[10] The two measures of socio-economic deprivation were not exactly the same, one measured the extent of food insecurity and the other the number of deprivations experienced. Therefore, the correlation coefficient between the two would not be expected to be very high. The aim was to test whether they were significantly correlated to provide confidence in the *money for food* deprivation measure, self-reported by the adolescents.

[11] For those students that had left school, questions about school were asked in the past tense, for example, 'How well did you get along with your teachers when you were at school?' and the answers combined with those students that were still at school.

were transformed using the non-paranormal transformation (Liu et al., 2009) with the R package Huge (Zhao et al., 2012) before being entered into the network analyses. The distributions of the depression symptoms were very skewed with very small cell counts (< 5 in some cases for the most severe symptom level) and so were entered into the networks as continuous numeric variables, after being transformed.

As the data contained categorical, ordinal and continuous numeric variables, mixed graphical models were used to fit the networks and estimate pairwise associations, using the R package *mgm*, which is suitable for the network modelling of data of different types (Haslbeck & Waldorp, 2015). In the networks, nodes represented the variables and edges the pairwise relationships between them (Borsboom & Cramer, 2013). The presence of an edge implied that two variables were associated, after conditioning on all other variables (Drton & Perlman, 2004). The networks were weighted and the edge weights, equivalent to partial correlation coefficients, calculated via nodewise regression (Haslbeck & Waldorp, 2015; Meinshausen & Bühlmann, 2006). To control for spurious edges, the networks were regularized using least absolute shrinkage and selection operator (LASSO) (Tibshirani, 1996), with model selection using Extended Bayesian Information Criterion (EBIC) (Foygel & Drton, 2010) plus a hyperparameter gamma (Chen & Chen, 2008; Foygel & Drton, 2010), all available through the mgm package (Haslbeck & Waldorp, 2015). Gamma was set at 0.25 for the main network models. For sensitivity analysis, network models were also fitted using a more conservative gamma value (0.5).

The mgm package (Haslbeck & Waldorp, 2015) integrates with the R package qgraph (Epskamp et al., 2012) to display the network as a graphical model. The package uses the Fruchterman-Reingold algorithm which places nodes with stronger connections closer together.

Network reliability was tested using 500 non-parametric bootstrap resamples (Haslbeck & Waldorp, 2015), to test how often an edge was recovered, that is how often an edge was estimated to be non-zero in the bootstrap samples. A rate of edge recovery at or close to 100% provides strong evidence that the association is reliable (Fried & Haslbeck, 2019; Haslbeck & Waldorp, 2015). Redundant nodes, nodes that are too topologically similar, can cause problems for network analysis. Therefore, the goldbricker function in R package NetworkTools (Jones, 2020) was used to identify redundant nodes.

The relative importance of the individual depression symptoms was tested using three common measures of node centrality: Strength, Betweenness, and Closeness. Strength is calculated by summing the edge weights for each node; Betweenness by counting the number of times a node lies on the shortest path between two other nodes; and Closeness by the average distance from a node to other nodes (Costantini et al., 2015). Nodes with high centrality are potentially

influential in the network and action affecting them could affect other nodes (Borsboom & Cramer, 2013).

3.3. Results

3.3.1. Descriptive Statistics

At the PIF Study 17-year data collection wave, 632 participants took part, but there were problems with missing data, particularly with the CDI:S, the variable measuring *Depression severity*, with 48% of participants having one or more items missing. After removing those participants with more than 30% of items missing on the CDI inventory, data were imputed using missForest (Stekhoven & Bühlmann, 2012) (See Chapter 2 Methods and Measures, section 2.2 Missing Data and Participant Exclusion for a more detailed description of the missing data analysis and imputation method). The final analytic sample included 561 participants. Participants excluded from the analysis had lower *Impulsivity* (P=0.034) and spent less time online (*Hours online*) (P=0.007) (P values calculated after adjusting for multiple testing using Holm) compared to those included, but there were no other significant differences between the two groups for the other explanatory variables. *Depression severity* scores were significantly lower in the analytic sample (P=0.002), compared with the full 17-year sample, as were symptom scores for *Cry* (P=0.003) (P values based on the Wilcoxon rank-sum test). See Table 6 for the summary characteristics of both the full year-17 and analytic samples.

The analytic sample included 297 males (51%), 276 females (49%), with 400 (71%) identifying as either Samoan or Tongan. Gender and ethnicity were both self-identified. These gender and ethnicity proportions are representative of the national average for Pacific youth aged 15-19 in NZ, however, those identifying as Cook Islands Māori or Other Pacific Island were underrepresented (Stats NZ, 2018). Around 8% of the analytic sample identified as being either NZ Pākehā, Māori, or all Pacific groups equally, as opposed to with one of the Pacific ethnic groups. Consistent with national statistics on food insecurity amongst Pacific families, this sample of Pacific adolescents suffered much higher food insecurity than NZ families generally, with 71% of this sample saying their parents worried about having enough money for food ‘Sometimes’, ‘Often’, or ‘Always’ compared with 22% of parents overall in NZ, based on data in a survey using a similar measure (Ministry of Health, 2019). The proportion of the sample still attending school at 17 was 87.9%, which was above the national average of 83.5% (Ministry of Education, 2020). *Depression severity* ranged from 10 (the lowest possible score) to 27 (close to the highest possible score of 30) in the analytic sample and the depression symptoms with the highest means were *Looks* followed by *Bothered*, and the lowest were *Love* and *Not enough friends*.

Table 6 Participant summary characteristics

Variables (variable name in italics)	Full year-17 sample, N=632	Analytic sample (after data imputation) n=561
Categorical variables	n (%)	n (%)
Gender[a]		
Female	297 (48.5%)	275 (49.0%)
Male	316 (51.5%)	286 (51.0%)
Missing	19	
Ethnicity		
Samoan	299 (47.5%)	269 (48.0%)
Tongan	153 (24.4%)	131 (23.4%)
Cook Islands Māori	92 (14.6%)	82 (14.6%)
Other Pacific Island[b]	38 (6.0%)	35 (6.2%)
Other[c]	47 (7.5%)	44 (7.8%)
Missing	3	
How often parents worry about having enough money for food (*Money for food*)		
Never	177 (30.1%)	165 (29.5%)
Sometimes	232 (39.4%)	234 (41.7%)
Often	88 (15.0%)	81 (14.4%)
All the time	91 (15.5%)	81 (14.4%)
Missing	44	
Do you still attend school (*Attend school*)		
Yes	554 (87.7%)	493 (87.9%)
No	78 (12.3%)	68 (12.1%)
Continuous variables	Mean (SD)	Mean (SD)
Average sum score of depression symptoms (*Depression severity*)	13.18 (3.10)	12.52 (2.79)
No. of participants missing (one item or more on depression inventory)	355	
How feels about looks (*Looks*), 1=I look okay, 2=There are some bad things about my looks, 3=I look ugly	1.49 (0.65)	1.49 (0.64)

How often bothered by things (*Bothered*) (r)[d], 1=Things bother me all the time, 2= Things bother me many times, 3= Things bother me once in awhile	1.48 (0.66)	1.46 (0.65)
Believes things will not work out (*Not work out*) (r)[d], 1=Nothing will ever work out for me, 2=I am not sure if things will work out for me, 3=Things will work out for me okay	1.34 (0.51)	1.33 (0.50)
How often feels like crying (*Cry*) (r)[d], 1=I feel like crying every day, 2=I feel like crying many days, 3=I feel like crying once in a while	1.26 (0.51)	1.17 (0.43)
How often feels alone (*Alone*), 1=I do not feel alone, 2=I feel alone many times, 3=I feel alone all the time	1.24 (0.50)	1.25 (0.50)
How often feels sad (*Sad*), 1=I am sad once in a while, 2=I am sad many times, 3=I am sad all the time	1.23 (0.46)	1.21 (0.45)
Does things right or wrong (*Does things wrong*), 1=I do most thing okay, 2=I do many things wrong, 3=I do everything wrong	1.20 (0.42)	1.20 (0.42)
How feels about self (*Self-hatred*) (r)[d], 1=I hate myself, 2=I don't like myself, 3=I like myself	1.15 (0.39)	1.15 (0.39)
Believes someone loves them (*Love*) (r)[d], 1=Nobody loves me, 2=I am not sure that anybody loves me, 3=I am sure that somebody loves me	1.14 (0.36)	1.13 (0.35)
Has enough or not enough friends (*Not enough friends*), 1=I have plenty of friends, 2=I have some friends, but I wish I had more, 3=I do not have any friends	1.13 (0.39)	1.13 (0.39)

[a]The gender data used in this study were self-identified and collected in the 14-year wave as no gender data were collected in the 17-year wave. Participants were given the options of male, female or pass/don't know. The response pass/don't know was treated as missing as cell counts for this response were very small.

[b] This group was made up of those who identified as Tokelauan, Niuean, or Fijian.

[c]This group was made up of those who identified as Pākehā (European New Zealanders), Māori or multiple groups equally.

[d]These items were reverse scored. After reverse scoring relevant symptoms, all higher scores corresponded to higher symptom severity.

3.3.2. Network Estimation

PCB and *Binge drinking* were identified by goldbricker in the R package NetworkTools (Jones et al., 2018) as being redundant nodes, that is they were too topographically similar to other nodes in the networks, namely to *CE and GME* in the case of *PCB* and to *Ever had sex* in the case of *Binge drinking* (see 3.2.3 Statistical Analysis section above). Therefore, *PCB* and *Binge drinking* were removed from the network analysis. Networks were also fitted with the full set of

analysis variables to test the impact of removing *PCB* and *Binge drinking* and the results were unchanged. See Appendix A for details of Tables A-3 to A-8, the weighted adjacency matrices for the depression severity and depression symptom networks and also for the full set of variables, with none removed.

3.3.3. Network Associations with Depression Severity

The variables associated with *Depression severity* in the main network model (gamma=0.25) were, with edge weights shown in brackets, *Part of school* (0.28), *Relationship with mother* (0.23), *Relationship with friends* (0.13), *Impulsivity* (0.14), *Gender* (0.11), *Energy levels* (0.16), and *Self-assessed weight* (0.04). See Figure 3 for the Depression severity network graph and Table 7 for the legend of node labels and explanatory variables. For *Part of school, Relationship with mother, Relationship with friends,* and *Gender*, the associations were negative, implying that a lack of school connectedness, lower scores on the relationship scales, or being female were independently associated with higher *Depression severity*. *Impulsivity* was positively associated, meaning higher *Impulsivity* scores were correlated with higher *Depression severity* scores.

For *Energy levels* and *Self-assessed weight,* the signs were undefined in the network graphs, but post hoc testing indicated that the two highest levels of *Self-assessed weight* ('a little overweight' and 'overweight') were associated with higher *Depression severity* scores, and for *Energy levels* the Depression severity scores increased as *Energy levels* decreased in a linear trend.

The edge *Relationship with mother—Depression severity* had the highest edge recovery rate. It was recovered in all the bootstrap samples (100% reliability), followed by *Impulsivity—Depression severity* (94%). The edges between *Depression severity* and *Energy levels*, *Relationship with friends*, and *Part of school* all had rates close to or over 80% and so were estimated somewhat reliably. The edges *Self-assessed weight—Depression severity* and *Gender—Depression severity* were estimated much less reliably, being recovered in just over half of the bootstrap samples.

When gamma was raised to 0.5, all edges with *Depression severity* remained, apart from the ones with *Gender* and *Self-assessed weight* which were shrunk to zero. See Table 8 for edge weights, direction of associations (where defined), and edge recovery rates of those explanatory variables associated with *Depression severity.*

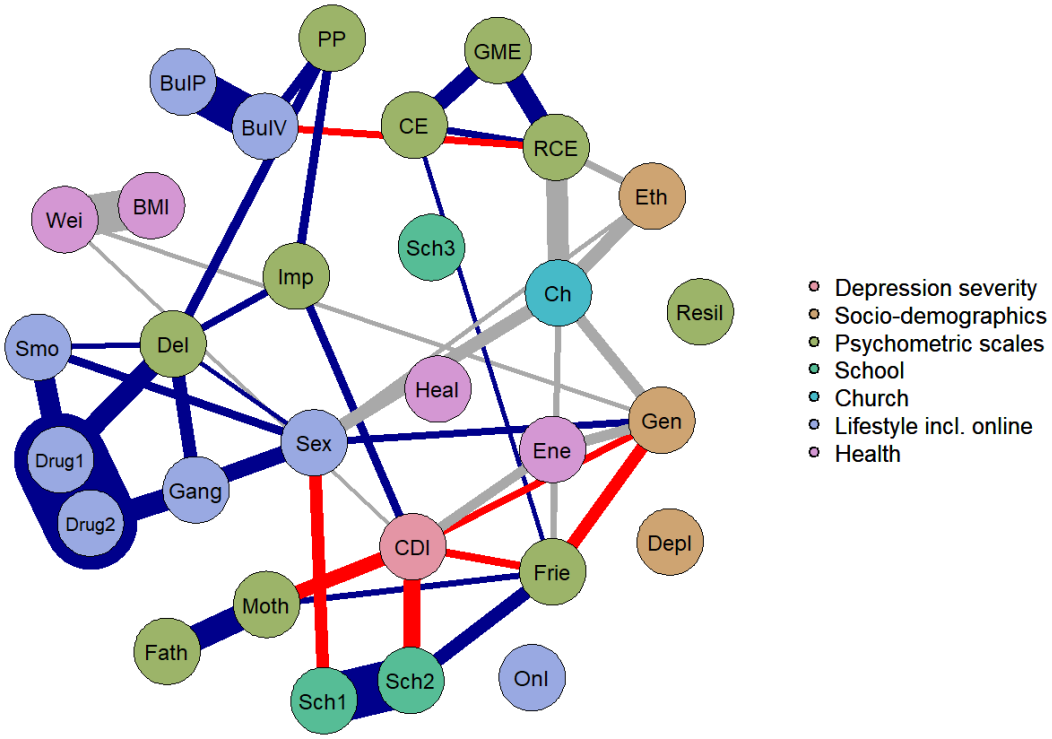

Figure 3 Network showing the relationships between Depression severity and the explanatory variables, gamma = 0.25, n=561

The width of the edges illustrates the strength of the association (wider edges depict stronger associations) and the colour the direction of the association between the two nodes. Blue represents a positive association, red a negative association, and grey means the sign is undefined in the network graph. See Table 7 for the legend of node labels and explanatory variables.

Table 7 Node labels and their corresponding explanatory variables for Figure 3 and Figure 4

Node	Variable	Node	Variable
CDI[a]	*Depression severity* - a sum score of symptoms	Moth	*Relationship with mother*. Higher scores = better relationship
Gen	*Gender* (0=Female, 1=Male)	Fath	*Relationship with father*. Higher scores = better relationship
Eth	*Ethnicity* (1=Samoan, 2=Tongan, 3=Cook Islands Māori, 4=Other Pacific Island, 5=Other)	Frie	*Relationship with friends*. Higher scores = better relationships
DepI	How often parents worry about having enough money for food (M*oney for food*) (1=Never, 2=Sometimes, 3=Often, 4=All the time)	CE	Cultural efficacy (*CE*). Higher scores = higher identification
Heal	*Health* (1=Poor, 2=Fair, 3=Good, Very Good, or Excellent)	GME	Group Membership Evaluation (*GME*). Higher scores = higher identification
BMI	Body mass index (*BMI*) (weight (kg) / height (m))2	RCE	Religious Centrality and Embeddedness (*RCE*). Higher scores = higher identification
Wei	*Self-assessed weight* (1=Underweight, 2=About right, 3=A little overweight, 4=Overweight)	Imp	*Impulsivity*. Higher scores = higher impulsivity
Ene	How often feels full of energy (E*nergy levels*) (1=All or most of the time, 2=Some of the time, 3=Little or none of the time)	Resil	*Resilience*. Higher scores = higher resilience
Ch	*Church attendance* (1=Never, 2=About once a year, 3=About once a month, 4=About once a week, 5=2 or 3 times week)	PP	*Negative peer influence*. Higher scores = higher susceptibility to negative peer pressure
Smo	*Smoke cigarettes* (0=Never, 1=Have tried)	Gang	*Gang involvement* (0= No, 1=Yes)
Onl	*Hours online* (per day) (1=0-2 hours, 2=3-4 hours, 3=5-6 hours, 4=7 or more hours	Del	*Delinquency*. Higher scores = higher level of delinquency
BulP	*Bullied online – perpetrator* (0=No, 1=Yes)	Sch1	*Attend school* (0=No, 1=Yes)
BulV	*Bullied online – victim* (0=No, 1=Yes)	Sch2	*Part of school* (0=No, 1=Yes)
Drug1	*Smoke marijuana* (0=No, 1=Yes)	Sch3	*Get along with teachers* (1=Usually, 2=Sometimes, 3=Hardly ever or Not at all)
Drug2	*Take legal highs* (0=No, 1=Yes)	Sex	*Ever had sex* (0=No, 1=Yes)

[a] CDI (Depression severity) was not included in the Figure 4 network graph as depression was measured in terms of individual depression symptoms. All explanatory variables were the same in Figure 3 and Figure 4.

Table 8 Edge weights and edge recovery rates for the Depression severity networks

Variables associated with *Depression severity*	Edge weights for different values of gamma, 0.25	0.5	Sign	Edge recovery rate[a]
Gender	0.11	0	-ve	56%
Relationship with mother	0.23	0.23	-ve	100%
Relationship with friends	0.13	0.12	-ve	86%
Impulsivity	0.14	0.11	+ve	94%
Self-assessed weight	0.04	0	na[b]	54%
Energy levels	0.16	0.11	na[b]	87%
Part of school	0.28	0.25	-ve	77%

[a]Edge recovery rates and Bootstrap quantiles were estimated with 500 resamples from the gamma=0.25 network model

[b]-ve means the association was negative, +ve means the association was positive and na means the sign for categorical variables with more than two levels cannot be defined in the network graph, but more information about the nature of the association was extracted from post hoc testing (see Network associations with Depression severity section above)

3.3.4. Network Associations with Individual Depression Symptoms

Relationship with mother shared an edge with the largest number of symptoms in the main network model (gamma=0.25), namely *Alone* (0.07), *Not work out* (0.09), *Sad* (0.07), and *Self-hatred* (0.10). *Relationship with friends* shared an edge with two symptoms: *Not enough friends* (0.13) and *Does things wrong* (0.04). *Delinquency*, *Part of school*, *Self-assessed weight*, and *Hours online* shared an edge with one symptom (see Figure 4 for the depression symptom network graph). Edge weights between depression symptoms and explanatory variables were generally much lower in the depression symptom network, with most edge weights between 0.04 to 0.10, except for *Part of School – Not enough friends* (0.29), followed by *Relationship with friends – Not enough friends* (0.13).

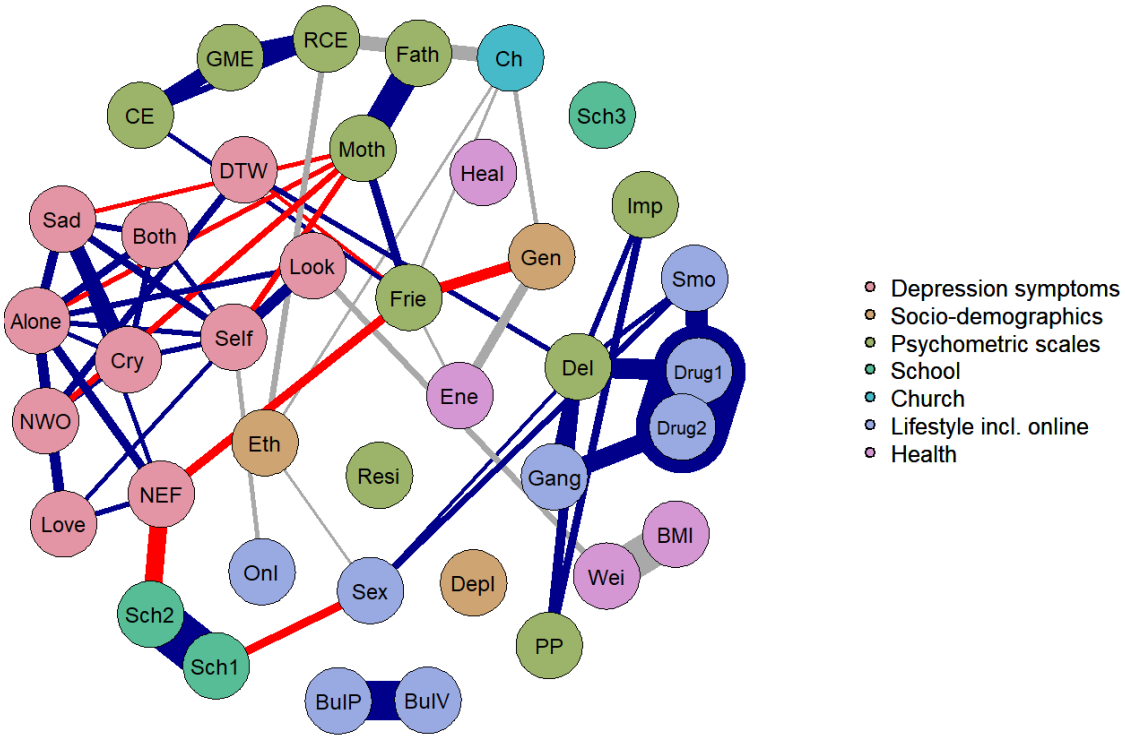

Figure 4 Network showing the relationships between individual depression symptoms and the explanatory variables, gamma = 0.25, n=561

The width of these edges illustrates the strength of the association (wider edges depict stronger associations) and the colour the direction of the association between the two nodes. Blue represents a positive association, red a negative association and grey means the sign is undefined in the network graph. Legend of node labels and depression symptoms: Alone (*Alone*), Sad (*Sad*), Cry (*Cry*), Look (*Look*s), Both (*Bothered*), NEF (*Not enough friends*), NWO (*Not work out*), DTW (*Does things wrong*), Self (*Self-hatred*), Love (*Love*). See Table 7 for the legend of the node labels and explanatory variables.

All associations between depression symptoms and *Relationship with mother*, *Relationship with friends*, and *Part of school* were negative, implying that lower scores on the relationship scales or a lack of School connectedness were independent risk factors for the symptoms they shared an edge with. The association between *Delinquency* and *Does things wrong* was positive, implying higher *Delinquency* scores were a risk factor for *Does things wrong*. The signs for *Self-assessed weight—Looks* and *Hours online—Self-Hatred* were undefined in the network graphs, but post hoc testing indicated that the two highest levels of *Self-assessed weight* ('a little overweight' and 'overweight') were risk factors for the symptom *Looks* and spending seven or more hours online was a risk factor for *Self-hatred*.

In terms of reliability, the highest edge recovery rate was for *Self-assessed weight – Looks* (92%), followed by *Relationship with mother—Self-hatred (78%)*, and *Relationship with friends*

– *Not enough friends* (78%). See Table 9 for edge weights and recovery rates of those variables associated with at least one depression symptom.

Table 9 Edge weights and edge recovery rates in depression symptom networks

Variables associated with depression symptoms	Depression symptoms	Edge weights for different values of gamma 0.25	0.5	Sign	Edge recovery rate[a]
Relationship with mother	*Alone*	0.07	0.07	-ve[b]	64%
	Sad	0.07	0.06	-ve	47%
	Self-hatred	0.10	0.09	-ve	78%
	Not work out	0.09	0.08	-ve	46%
Relationship with friends	*Not enough friends*	0.13	0.11	-ve	78%
	Does things wrong	0.04	0.03	-ve	27%
Delinquency	*Does things wrong*	0.08	0.07	+ve[b]	51%
Self-assessed weight	*Looks*	0.08	0.08	na[b]	92%
Part of school	*Not enough friends*	0.29	0.22	-ve	64%
Hours online	*Self-hatred*	0.05	0.05	na[b]	53%

[a]Edge recovery rates and Bootstrap CIs were estimated with 500 resamples from the gamma=0.25 network model

b -ve denotes a negative relationship, +ve a positive relationship, and na means the sign for categorical variables of more than two levels cannot be defined in the network graph, but more information about the nature of the association was extracted from post hoc testing (see 3.3.4 Network associations with individual depression symptoms section above)

3.3.5. Centrality

Centrality measures were calculated for the depression symptoms. *Alone* had the highest centrality score by far, for all three measures (Strength, Betweenness, and Closeness) followed by *Self-hatred* and *Sad*, whose scores were almost identical for Strength. *Self-hatred* had a slightly higher Betweenness score and *Sad* a slightly higher Closeness score. See Figure A-1 in Appendix A.

3.4. Discussion

Relationship with mother, Relationship with friends, Part of school, Delinquency, Self-assessed weight, and *Hours online* were all associated with at least one depression symptom, but the symptoms they were associated with varied substantially. Some symptoms, for example, *Cry* or

Love were not associated with any explanatory variables. These findings support the network model of psychopathology that depression symptoms are not all equal in terms of their impact on depression and that potentially clinically valuable information is lost in terms of possible symptom specific interventions when depression is measured as a sum score (Borsboom, 2008; Borsboom & Cramer, 2013; Fried & Nesse, 2015b; McNally, 2016). Variable associations between depression symptoms and risk factors have been shown in other studies with adults (Lux & Kendler, 2010), including in a network analysis with young adults (Fried et al., 2014), but to the author's knowledge this is the first study to show this amongst adolescents.

A poor-quality mother-child relationship was arguably the highest risk factor for depression for this group of Pacific adolescents. In the Depression severity network, *Relationship with mother* was the only explanatory variable to have an edge recovery rate of 100%. Other studies have also found that the quality of parental relationships and level of family functionality are important determinants of childhood and adolescent depression (Nishikawa et al., 2010; Paterson et al., 2014). In the depression symptom networks, *Relationship with mother* was associated with four symptoms, but only two of these associations were reliable (based on edge recovery rates), *Relationship with mother—Self-hatred* and *Relationship with mother—Alone*. These two symptoms also had the highest centrality scores (along with *Sad*). Based on the network model of psychopathology, that depression symptoms are likely to be causally related and reinforcing and triggering each other, it has been argued that designing interventions aimed at symptoms with high centrality could have many beneficial knock-on effects for other symptoms (Borsboom & Cramer, 2013). *Relationship with father* was indirectly negatively associated with both *Depression severity* and depression symptoms, through its positive correlation with *Relationship with mother*, and so was also important in terms of depression risk. The findings from this study and others emphasize the importance of quality parental (or primary caregiver) relationships at all stages of a child's life.

High quality relationships with friends and School connectedness came through consistently and reliably as protective factors against depression, and vice versa, that is poor quality or lack of friendships or absence of School connectedness were risk factors. Other research into adolescent depression has also found similar links between the strength of close friendships and more positive outcomes, including more resilience and less depression symptoms (Bukowski et al., 1996; Narr et al., 2019). The association between school-related factors and adolescent depression supports findings from other studies (Kim et al., 2021; Paterson et al., 2014), including in recent meta-analyses (Clayborne et al., 2019; Finning et al., 2019; Tang et al., 2019). What is perhaps more noteworthy in this study is how important friends were to feeling part of school and the strength of the associations between school connectedness, friends, and depression. *Relationship with friends* and *Part of school* were both negatively associated with

Depression severity and the symptom *Not enough friends*. *Not enough friends* was the only symptom to be reliably associated with two explanatory variables. The edge weights for *Part of school–Depression severity* and *Part of school–Not enough friends* were the highest in their respective networks. Another school related variable, *Get along teachers*, was not associated with either *Depression severity* or any depression symptoms. A network analysis of symptoms of depression amongst Korean preadolescents found a strong association between school dislike and lack of friendship (Kim et al., 2021), yet a network study with US adolescents using the same symptom items did not (Mullarkey et al., 2019). The authors of the Korean study theorised that, compared to their American peers, Korean children may be more likely to develop depression because of a fall out with friends or lack of friendships because of the more collectivist culture in East Asian countries (Kim et al., 2021). There is some empirical evidence that Pacific people hold more collectivist views than NZ Europeans (Podsiadlowski & Fox, 2011), and this could be, at least in part, responsible for the strong relationships between school connectedness, friendships and depression. Depression was indirectly negatively associated with *Attend school* through the positive association between *Attend school* and *Part of school*. The results from this study imply that maintaining positive friendships could be an important factor in continuing to attend secondary school and so could be a focus for any programmes aiming to keep adolescents at school for longer; although this study was cross-sectional, so causality cannot be assumed.

Impulsivity was positively associated with *Depression severity* for both gamma values and with a high level of reliability and this supports findings from other adolescent depression studies (Piko & Pinczés, 2014; Regan et al., 2019), plus a recent meta-analysis that found that self-regulation (similar to impulsivity) in childhood was a predictor of depressive symptoms in adulthood (Robson et al., 2020). Furthermore, in the Depression severity networks, *Impulsivity* was the bridging node between *Depression severity* and *Delinquency* (and *Negative peer influence).* Based on evidence that has shown that targeting bridging nodes may cut connections with undesirable outcomes (Jones et al., 2018; Solmi et al., 2020), planning interventions that reduce impulsivity could potentially have many beneficial consequences, including reducing the risks for the development of depression and engaging in delinquent behaviours. In the depression symptom networks, *Delinquency* was a risk factor for the depression symptom *Does things wrong* and *Impulsivity* was indirectly associated with this symptom through its positive association with delinquency. Encouraging more self-reassurance and less self-criticism has been found to be protective against depressive symptomatology for adolescents (Barcaccia et al., 2020). However, this study was cross-sectional, so the direction of the association is unknown, also the reliability of the *Delinquency—Does things wrong* edge was low. Future longitudinal studies could help identify causality, with respect to impulsivity, delinquency, and depression.

Gender was weakly associated with *Depression severity*: the edge recovery rate for *Gender–Depression severity* was low, and this edge disappeared in the gamma=0.5 network model. *Gender* was also not directly associated with any depression symptoms but was indirectly associated with the symptom *Not enough friends*. Based on results of past studies (Carlson & Cantwell, 1980; Ivarsson et al., 2006; Kandel & Davies, 1982; Maughan et al., 2013; Paterson et al., 2018) and results from NZ surveys, (see 3.1 Introduction) (Fleming et al., 2020), the expectation may have been for a stronger association between *Gender* and depression in the networks. The relatively weak association (between *Gender* and the depression measures) in this study could be the result of the conditional dependencies the network models are based on. Some of the explanatory power of *Gender* appears to have been reduced due to *Gender*'s shared variance with other factors, several of which were very significantly correlated with *Depression severity* and depression symptoms. See Appendix A for details of Tables A-9 to A-12, the zero-order correlation matrices of the analysis variables in the depression networks and the associated P values (unadjusted for multiple testing).

Energy levels had a relatively strong relationship with *Depression severity,* in terms of edge recovery rates and edge presence for both gamma values (0.25 and 0.5). Associations between fatigue and depression are supported in other studies (Lundervold et al., 2013) and it is a common presenting symptom of those with Major Depressive Disorder (Targum & Fava, 2011). It was not associated with any depression symptoms, however, which was most likely because of the variance it shared with a number of other variables, reducing its explanatory power. For example, in the zero order correlation matrices, *Energy levels* was significantly associated with every depression symptom. See Appendix A for details of Tables A-9 to A-12, the zero-order correlation matrices of the analysis variables in the depression networks and the associated P values (unadjusted for multiple testing). These are supplied in a separate electronic file due to the large size of some of the tables.

Self-assessed weight was weakly associated with *Depression severity* but had a more reliable and consistent relationship with the depression symptom *Looks*: it had the highest edge recovery rate amongst the associations with symptoms (92%) and the edge was maintained when gamma was raised to 0.5. Interventions targeting dissatisfaction with body image have been proven to decrease depressive symptoms in both sexes (Bearman et al., 2003).

Online hours was associated with the symptom *Self-hatred*, and other studies have also found screen time (Boers et al., 2019) or social media use (Riehm et al., 2019) are risk factors for adolescent mental health, but the edge recovery rate for this association was low, so this finding is not really interpretable without replication.

Neither *Money for food*, the deprivation indicator, or *Resilience* were found to be associated with *Depression severity* or any depression symptoms, which goes against findings from other studies (Carbonell et al., 2002; Lorant et al., 2007; Ostler et al., 2001; Poole et al., 2017; Remes et al., 2019; Skrove et al., 2013) including NZ health statistics (Ministry of Health, 2021a). The lack of association in this study could be because the sample was relatively homogeneous, both in terms of residential area and individual deprivation (see section 3.2 Methods, subhead 3.2.1 Source of Data and Participants, and section 3.3 Results, subhead 3.3.1 Descriptive Statistics). A study by Fagg et al (2006) also found no significant associations between material deprivation and mental illness and they thought the reason might lie in the low level of socio-economic disparity in their sample (Fagg et al., 2006). It is not clear why *Resilience* was not associated with any depression measures. It was associated with *Depression severity* in the zero-order correlation matrix (see Appendix A for details of Tables A-9 to A-12), but even then, only weakly. Perhaps the inventory used to measure *Resilience* did not capture the true variability of this construct across the sample, but more investigation would be needed before any final conclusions are drawn.

3.5. Limitations

One of the main limitations of the current study was its cross-sectional design, meaning causality could not be established. It was also largely exploratory and was not testing any hypotheses, but it did have clear aims. Most of the variables were self-reported and there were issues with missing data. These issues were partially overcome by removing participants with too much missing data and imputing with a suitable multiple imputation method, but the participants removed from the analysis had, on average, lower impulsivity, and spent less time online. The *Depression severity* scores and scores for the symptom *Cry* were higher in the full year-17 sample (N=632) compared to the analytic sample (n=561). The community sample was relatively homogeneous in terms of age, socio-economic status, and ethnicity, so may not generalize to other populations or clinical samples.

3.6. Conclusion

This study used network analysis to discover the risk factors for depression amongst a sample of Pacific adolescents. It measured depression both as a single latent construct and in terms of individual symptoms. The results showed that there was much variation in terms of how risk factors presented in terms of symptoms. Measuring depression in terms of a single construct is still important for diagnostic purposes, for example, but much potentially useful information is lost if only the sum of depression symptom scores is used. Most of the associations with depression identified in this study, such as *Relationship with mother*, *Relationship with friends*, *School connectedness*, and *Impulsivity*, support those from other studies (Bukowski et al., 1996;

Narr et al., 2019; Nishikawa et al., 2010; Paterson et al., 2018; Piko & Pinczés, 2014; Regan et al., 2019; Tang et al., 2019), but this study identified associations with these risk factors at the symptom level, and this additional information could be useful in helping to shape treatment strategies and tailor make intervention programmes, for individuals or groups based on their risk factor - depression symptom profiles.

Prelude Chapter 4

This chapter examined associations between individual depression symptoms with suicidality amongst NZ Pacific adolescents using network analysis, by fitting a series of network models. The first model included only individual depression symptoms with suicidality; the second additionally included self-harm; and the third included self-harm plus a wide range of relevant multi-dimensional variables, It has been published in Suicide and Life-Threatening Behaviour (Gossage et al., 2023)

Chapter 4. Chapter 4 Understanding the Relationships between Depression Symptoms, Self-harm, and Suicidality in Pacific NZ Adolescents?

4.1. Introduction

According to the WHO, suicide is the fourth leading cause of death amongst 15–19-year-olds (WHO, 2020). This problem is particularly acute in NZ (NZ), which had the highest teen (aged 15-19) suicide rate in the Organisation for Economic Co-operation and Development (OECD), in a 2017 report (OECD, 2017). A recent investigation into youth mental health in NZ referred to adolescents as experiencing a rising "pandemic of psychological distress" (Menzies et al., 2020, p2).

Suicidal thoughts, plans, and attempts are consistent predictors of future suicide attempts (Coppersmith et al., 2017; Franklin et al., 2017; Goldston et al., 1999), and suicidal thoughts and attempts have been found to predict suicide death (Beghi et al., 2013; Bilsen, 2018; Chan et al., 2016; Franklin et al., 2017; Hubers et al., 2018). Therefore, a better understanding of suicidal thoughts, plans and attempts, defined in this study as suicidality, is the prerequisite of any effective suicide prevention strategy. Indeed, Jobes and Joiner (2019) believe more interventions should be directed at suicide ideation as an intervention target, independently of suicide attempts. Reinherz et al. (2006) found that those with suicide ideation in adolescence were 12 times more likely to have attempted suicide by the time they were 30, compared to those without suicide ideation. Although the overwhelming majority of those who think about, plan or attempt suicide do not usually die by suicide, suicidality is associated with many behaviours that significantly impact health and quality of life, such as substance abuse, aggression, irritability, and higher school dropout rates (Bousono et al., 2017; Daniel et al., 2006; Miotto et al., 2003; Orri et al., 2019).

4.1.1. The Pacific Population in NZ

The Pacific population in NZ comprises those whose heritage traces back to various Pacific islands, with the largest groups from Samoa (48%), Tonga (22%), and the Cook Islands (21%), and also includes Niue (8%), Fiji (5%), Tokelau (2%), Tuvalu Islands (1.2%), and Kiribati (0.8%) (Statistics NZ, 2018). Overall, around 8% of the NZ population identify as being of Pacific origin. The Pacific population in NZ is highly urbanized, with around two thirds living in the Auckland region, and youthful, with a median age of 23 years compared with 38 years for the NZ national average (Statistics NZ, 2018). Pacific people in NZ are generally more religious than New Zealanders overall, with 23% of Pacific New Zealanders stating they have no religion, compared to the national average of 48%. Pacific New Zealanders maintain strong cultural roots with their Pacific homelands, and although each island community has its own distinct

characteristics, Pacific people share several cultural values, including spirituality, collectivism, importance of family, and behaving respectfully, particularly towards elders and people in positions of authority (Ministry for Pacific Peoples, 2022). They add a vibrance and cultural richness to NZ in many ways, including but not limited to their contributions to music and art, and their celebrations of pan-Pacific culture through the festivals Polyfest, which also celebrates Māori culture, and Pasifika Festival. Unfortunately, they experience socio-economic deprivation at above average levels; for example, they are over-represented in the Auckland's poorest suburbs (Ministry of Health, 2021) and a recent survey found that 37% of Pacific children live in severe to moderate food insecure households compared to 19% for NZ children overall (Ministry of Health, 2019). Pacific adolescents in NZ are vulnerable to suicidality, particularly suicide attempts, and are around three to four times more likely to report attempted suicide than NZ European adolescents[12] (Fa'alili-Fidow et al., 2016; Fleming et al., 2020). They also have higher rates of reported suicide plans (Fortune, 2010) and are much less likely to access professional medical help (Helu et al., 2009).

4.1.2. Risk Factors for Suicidality

As with other mental disorders, suicidality appears to result from the complex and dynamic interplay of factors from across many life domains, rather than as the result of a single stressor (Fonseca-Pedrero et al., 2022). Findings from published studies are often contradictory and it has been suggested that conflicting results could be the result of indirect associations and comorbidity (Goldston, 2004; Hawton et al., 2012). However, depression and deliberate self-harm have been consistently associated with adolescent suicidality in both cross-sectional and longitudinal research (Bilsen, 2018; Galaif et al., 2007; Goldston et al., 1999; Macalli et al., 2021), including in a large meta-analysis (Gillies et al., 2018). Furthermore, the association strengthens as incidences of self-harm increase (Gillies et al., 2018).

Other factors commonly found to be associated with adolescent suicidality include psychological disorders and problems, such as anxiety and hopelessness (e.g. Ayub, 2009; Elledge et al., 2021; Hill et al., 2011; Macalli et al., 2021); low self-esteem (e.g. Fonseca-Pedrero et al., 2020; Macalli et al., 2021), health risk behaviours (such as substance use and sexual activity) (e.g. Bilsen, 2018; Hallfors et al., 2004; Kuroki, 2015), behavioural issues (such

[12] Māori adolescents in NZ are also more likely to report attempted suicide compared to NZ Europeans (Fleming, T., Tiatia-Seath, J., Peiris-John, R., Sutcliffe, K., Archer, D., Bavin, L., Crengle, S., & Clark, T. (2020). Youth19 Rangatahi Smart Survey, initial findings: Hauora hinengaro/emotional and mental health. *The Youth19 Research Group, The University of Auckland and Victoria University of Wellington, NZ.*, ibid). Whilst this is of concern, Māori adolescents are not the focus of this research.

as impulsivity and delinquency) (e.g. Bilsen, 2018; Fonseca-Pedrero et al., 2022; Hawton et al., 2012), low socio-economic status (e.g. Navarro et al., 2021), bullying (e.g. Fonseca-Pedrero et al., 2022), a lack of connectedness with family, friends, school, and peers (e.g. Bilsen, 2018; Consoli et al., 2013; Whitlock et al., 2014), pain (Hinze et al., 2019), and poor self-rated health (Nkansah-Amankra et al., 2010). Teevale et al. (2016) found that risk factors for suicide attempts amongst Pacific adolescents in NZ were being female, food insecurity, poor family connections and monitoring, life dissatisfaction, having a religious affiliation, and having a family member or friend attempt or die by suicide. Conversely, higher levels of family monitoring were found to be protective (Teevale et al., 2016). Another study, using data from Pacific adolescents presenting at hospital after a suicide attempt, found that family or relationship stress were major precipitants for suicide attempts amongst Pacific adolescents in NZ (Aoelua, 2018).

4.1.3. The Network Approach to Psychopathology

Networks are a highly visual and versatile graphical tool, consisting of nodes and edges, suitable for displaying and investigating complex interactions amongst groups of variables that operate like systems (Barabási, 2012). For example, using network analysis, relationships amongst the explanatory variables can be identified as well as, direct and indirect associations with variables of interest (De Beurs et al., 2019). The use of network analysis in the field of psychology has gained traction over the last 10 years, inspired by the development of the network approach to psychopathology (Borsboom, 2017; Borsboom & Cramer, 2013) and advances in the development of statistical models and software (Epskamp, 2020; Haslbeck & Waldorp, 2020; Williams & Mulder, 2020). In psychological networks, nodes represent the study variables and edges the pairwise conditional relationships between them (Borsboom et al., 2021). According to the network approach to psychopathology, the symptoms and their interactions constitute the mental disorder, rather than being the manifestations of a common, underlying cause (Borsboom, 2017). The impact of symptoms on mental disorders is very heterogeneous (Fried et al., 2014; Gossage et al., 2022; Lux & Kendler, 2010). In a study on the effect of individual depression symptoms on psychosocial impairment, for example, Fried & Nesse (2014) found that the relative importance of symptoms (as measured by contribution of variance explained) on impairment ranged from 20.9% for Sad mood to 0.7% for Hypersomnia. Consequently, summing symptom scores to create a single latent construct leads to a loss of potentially valuable information and insight that could be used to aid the design of interventions (Borsboom & Cramer, 2013; Fried & Nesse, 2015b).

The present study used network analysis to gain a deeper understanding of how individual depression symptoms and self-harm contributed to suicidality in a sample of Pacific NZ adolescents, whilst allowing for the impact of a wide range of multidimensional variables

(variables related to family, school, health, socio-economic factors, risky behaviours, church, Pacific identity, resilience, behavioural problems, internet use, and peer relationships) found to be associated with suicidality in previous research (see 4.1.2 Risk factors for Suicidality).

Network models have been shown to differ amongst races/ ethnicities (Christian et al., 2021; Kim et al., 2021; Wasil et al., 2020). For example, in a study using network analysis to investigate depression symptoms and substance use amongst Indian adolescents, Wasil et al. (2020) found that the symptom relating to 'Feeling like a failure' had a much more central role than in another similar study with U.S. adolescents (Mullarkey et al., 2019), where 'Self-hatred' occupied a more central position. Wasil et al. (2020) proposed that it was the more collectivist culture in Indian society coupled with family pressure to achieve that was driving this difference. Kim et al. (2021), in a study of depression symptom networks among Korean children and adolescents, also believed that the more collectivist culture in South Asian countries was resulting in symptoms relating to school difficulties being more central in their network compared to the study by Mullarkey et al. (2019). Therefore, if network analysis is to fulfil its potential as an aid to clinical decision making, these decisions need to be based on culturally and ethnically relevant networks.

The key contributions of this work are twofold. Primarily, it is the first time that network analysis has been used to investigate suicidality in Pacific adolescents, inside or outside NZ, to date. Secondly, to date this is the first study to use network analysis to investigate the impact of self-harm and individual depression symptoms on adolescent suicidality, whilst conditioning on such a diverse set of variables, variables covering almost every aspect of an adolescent's life. Including a wide range of relevant variables reduces the risk that an association between two variables is really the result of both variables being associated with a third variable, that is absent from the network (Jones et al., 2017). This study is exploratory in nature and not associated with a formal hypothesis.

4.2. Methods

4.2.1. Sample

The present study used data collected during the 17-year wave of the Pacific Island Families (PIF) Study, between 2017 and 2018, when the participants turned 17. The PIF study is an ongoing longitudinal study of a birth cohort of 1398 Pacific children born at a South Auckland hospital in NZ in the year 2000 (Paterson et al., 2008). Eligibility criteria for the PIF Study included having at least one parent who identified as being of a Pacific ethnicity and was a permanent resident of NZ. The PIF Study has been guided by the Pacific People's Advisory Group and approved by Auckland University of Technology Ethics Committee (AUTEC)

(references 17/26 and 19/364 apply). To date, data have been collected at regular intervals from 6 weeks to 20 years of age.

Of the 632 participants who took part in the 17-year wave of the PIF Study, 82 participants were excluded due to having missing data for more than 30% of items on the psychometric inventories used, leaving a final sample of 550 participants. Data was imputed on the remaining missing data points using a multiple imputation method missForest (Stekhoven & Bühlmann, 2012) (see Appendix B Table B-1 for more details of participant characteristics pre and post data imputation, and Chapter 2 Methods and Measures, section 2.2 Missing Data and Participant Exclusion for more information on missing data analysis and the imputation strategy).

4.2.2. Measures

This study used a binary measure of *Suicidality*[13] based on the self-report answers to three questions:

1) "Have you seriously thought about killing yourself (attempting suicide)?"

2) "Have you made a plan to kill yourself (attempt suicide)?"

3) "Have you tried to kill yourself (attempted suicide)?"

Possible responses were "Not at all", "Not in the last 12 months", "Once or twice", or "Three or more times". If the responses to all three questions were "Not at all" or "Not in the last 12 months" then participants were coded as 0 for *Suicidality*; all other responses were coded as 1. The restriction to the last 12 months was to keep the time frame consistent with the question relating to *Self-harm,* and the collapsing of the levels "Once or twice" with "Three or more times" was due to small cell counts in the final level ("Three or more times").

Self-harm was measured as a separate construct to *Suicidality*, as definitions of what constitutes self-harm has a cultural contextual. For Pacific people in NZ, it may include harm to mental or spiritual self, as well as deliberate harm to the physical self (Dash et al., 2017). It was assessed with a single question: "During the last 12 months, have you deliberately hurt yourself or done anything you knew might have harmed you (but not kill you)? Answers were grouped into 3 levels: Level 1= No, Level 2=Once, and Level 3=Two times or more.

Depression was assessed using the shorter version of the Children's Depression Inventory (CDI:S) (Kovacs & Preiss, 1992) and analysed in terms of individual symptoms. The CDI:S is a

[13] When variables from this study are referred to in the text, they are denoted by capital first letter and italics, for example *Suicidality*, to differentiate them from general use of such terms and constructs.

ten-item, reliable depression scale suitable for youths aged 7 to 17 years (Klein, Dougherty, & Olino, 2005). Participants were asked to score each item from 1 to 3 to reflect how they felt about the item over the last two weeks. After reverse scoring positively worded items, higher symptom scores denoted higher symptom severity.

The socio-demographic variables of *Gender*, *Ethnicity*, and socio-economic deprivation were included in the study. The level of socio-economic deprivation was assessed with a self-reported measure of food insecurity, *Money for food* (Ramsey et al., 2012), where participants were asked how often their parents or guardians ever worried about having enough money to buy food. Due to the nature of the cohort, all participants were very close in age (M = 17.0, SD = 0.35), therefore age was not included as a variable. All these socio-economic variables were modelled as categorical.

The following variables were measured using psychometric inventories: *Relationship with mother, Relationship with father, Relationship with friends, Impulsivity, Delinquency, Negative peer influence, Gang involvement, Resilience*, and Pacific identity, which was measured with the following subscales: Cultural Efficacy (*CE*), Group Membership Evaluation (*GME*), Religious Centrality and Embeddedness (*RCE*), and Pacific Connectedness and Belonging (*PCB*). All these variables were modelled as continuous, with higher scores denoting a higher endorsement of the construct, apart from *Gang involvement*, which was binary, with a score of 1 corresponding to a "Yes" for *Gang involvement*. Confirmatory Factor Analysis (CFA) was performed on the items making up each inventory, using the R package Lavaan (Rosseel, 2012), to check whether they supported a single factor solution or a set of subscales. See Appendix B, Table B-2 for the results of the CFA.

Other variables used in the analysis *included Church attendance, Binge drinking, Smoke cigarettes, Take drugs*, (for example, party pills, smoke marijuana), *Had sex, Hours online, Online bullying - victim, Online bullying - perpetrator, Attend school, Part of school*[2]*, Get along with teachers*[14], Body mass index (*BMI*), *Health, Energy level*s, and *Self-assessed weight*. All these variables were modelled as categorical, apart from *BMI*, which was continuous. Weight and height measurements, used to calculate *BMI*, were taken by the study assessors, otherwise all data were self-reported by the adolescents but in the presence of trained Pacific assessors.

[14] For those students that had left school, questions about school were asked in the past tense, for example, 'How well did you get along with your teachers when you were at school?' and the answers combined with those students that were still at school.

4.2.3. Statistical Analysis

Statistical analysis was completed using statistical software R (R Core Team, 2020) augmented by various R packages, with alpha = 0.05 being the statistical significance threshold, where relevant.

4.2.3.1. Missing Data

The Kolmogorov-Smirnov (KS) test was used to compare the distributions of continuous variables, pre and post imputation (Abayomi et al., 2008) and Pearson's chi-square test of homogeneity for categorical variables (Reis et al., 1999).

4.2.3.2. Bivariate Tests

Bivariate associations with *Suicidality* were investigated using the two sample Wilcoxon Rank Sum test for the continuous variables (which all had moderate to severe skewed distributions) (See Appendix B Figure B-1 for histograms of the continuous variables), and Pearson's chi-square test for categorical variables. Multiple testing was adjusted using the Holm-Bonferroni method (Holm, 1979).

4.2.3.3. Network Estimation and Visualization

Cross sectional network analysis was used to identify conditional, pairwise associations amongst the study variables. As the data contained categorical, ordinal, and continuous numeric variables, mixed graphical models, were used to estimate the networks using the R package *mgm*, which is suitable for the network modelling of data of different types (Haslbeck & Waldorp, 2020). If two nodes shared an edge there existed a statistical relationship between them, conditional on all other variables in the network. "Conditional on all other variables" in this context means that an edge between two variables cannot be explained away by any of the other variables included in the network[15]. If they did not share an edge, they were conditionally independent. The mgm-package uses neighbourhood nodewise regression to estimate parameters, which are then combined into an edge weight (w), an absolute value that quantifies the strength of an association (see Chapter 2 Methods and Measures, section 2.5 Data Analysis, subheading 2.5.1 Network Estimation, subheading 2.5.1.2 Estimation of Edge Weights for more details of how the parameters are combined into edge weights). To control for spurious edges, mgm uses least absolute shrinkage and selection operator (LASSO) (Tibshirani, 1996); small edge weights are shrunk to zero via a penalty parameter lambda, and non-zero estimates are

[15] For example, if we have a chain graph A-B-C, then A and C are marginally dependent through B. However, when conditioning on all other variables (here only B), then A and C are conditionally (on B) independent. For more information on conditional independence see Dawid, A. P. (1979). Conditional independence in statistical theory. Journal of the Royal Statistical Society: Series B (Methodological), 41(1), 1-15.

shown by the presence of an edge. In this study lambda was selected using 10-fold cross validation (CV) (Haslbeck & Waldorp, 2020).

The network models were visualized using the R package qgraph (Epskamp et al., 2012). Blue edges depicted positive associations, red edges negative ones, and grey edges showed that the nature of the association could not be displayed in the network graph (because it involved a categorical variable with three levels or more) but could be discerned with post-hoc investigation. Odds ratios were used to estimate the characteristics of the association between *Suicidality* and *Self-harm*, as is common with binary and categorical variables (Szumilas, 2010). Node placement was controlled using Fruchterman-Reingold algorithm, which aims to place highly connected nodes at the centre of the network (Fruchterman & Reingold, 1991).

Before fitting the networks, continuous variables were transformed using a non-paranormal (npn) transformation (Liu et al., 2009), as their distributions were skewed (See Appendix B, Figure B-1), including all depression symptoms which were modelled as continuous, using the R package Huge (Zhao et al., 2012). Therefore, the associations shown in the networks involving continuous variables relate to the transformed data. Goldbricker function in the R package networktools (Jones, 2020) was used to test for redundant nodes; these are nodes that are too topologically similar to each other, which can interfere with network estimation accuracy (See Chapter 2 Methods and Measures, section 2.6 Data Analysis, subhead 2.6.1 Network Estimation, subhead Identify Redundant nodes using Goldbricker for more details on how goldbricker identifies redundant nodes).

4.2.3.4. Nodewise Predictability

Nodewise predictability was computed using methods available in the mgm package (Haslbeck & Waldorp, 2018). Predictability captures how well a given node can be predicted by its neighbours. For continuous variables, nodewise predictability was measured using R-squared, and for categorical variables it was measured both in terms of classification accuracy for the whole model, which includes the intercept model, and the additional accuracy over and above the intercept model, that is attributable to neighbouring nodes[16] (see Chapter 2 Methods and

[16] Predictability of a node by neighbouring nodes is the same as the predictability of a node by all nodes in the network. This is because all nodes that are not in the neighbourhood of given node have a zero-weight associated to them (Haslbeck, J. and L.J. Waldorp, How well do network models predict observations? On the importance of predictability in network models. Behavior Research Methods, 2018. 50(2): p. 853-861).

Measures, section Data Analysis 2.6, subhead 2.6.1 Network Estimation, subhead Network Node Predictability and Centrality).

4.2.3.5. Network Reliability

Pairwise edge reliability was assessed by calculating edge inclusion probabilities derived from 200 non-parametric bootstrap samples (Haslbeck & Waldorp, 2020). A high inclusion probability of a given edge across bootstrap samples provides evidence for this edge being present in the population (Fried & Haslbeck, 2019; Haslbeck & Waldorp, 2020). In addition to inclusion probabilities, we also summarized the bootstrapped sampling distributions by calculating quantiles, which allow one to get a more detailed picture of the accuracy of the parameter estimates. However, bootstrap quantiles from LASSO estimates cannot be interpreted in the same way as a traditional confidence interval, where a zero indicates that the true estimate is not different to zero, because LASSO estimates are biased towards zero (Bühlmann et al., 2014; Epskamp et al., 2018). Therefore, probability inclusion rates were used to discern the robustness of a pairwise association. The width of a bootstrap quantile, however, can be used to give a measure of parameter accuracy (Epskamp et al., 2018).

4.3. Results

Overall, 17.1% of the analysis sample reported *Suicidality*. This variable broke down as follows: suicidal thoughts 16%, suicide plans 9.8%, and suicide attempts 5.5% (there was overlap between these categories and so they do not sum to 17.1%). *Suicidality* primarily consisted of those having suicidal thoughts (94.2%). The majority of those reporting *Suicidality* were female (64%). Around 21% of the analysis sample reported self-harming once or more in the last 12 months, with females making up 62% of these.

See Table 10 for the summary characteristics of the analysis sample. There were no differences between the original sample (N=632) and the analysis sample (n=550), based on the results of the KS test and Pearson's chi-square test (see Appendix B, Table B-1).

Table 10 Participant summary characteristics

Variables (variable name)	Analysis sample[a] n=550
Demographics	n (%)
Gender[b]	
Female	270 (49.1%)
Male	280 (50.9%)
Ethnicity	
Samoan	263 (47.8%)
Tongan	129 (23.5%)
Cook Islands Māori	80 (14.5%)
Other Pacific Island[c]	35 (6.4%)
Other[d]	43 (7.8%)
How often parents worry about having enough money for food (*Money for food*)[e]	
Never	162 (29.5%)
Sometimes	228 (41.4%)
Often	82 (14.9%)
All the time	78 (14.2%)
Do you still attend school (*Attend school*)	
Yes	483 (87.9%)
No	67 (12.1%)
Depression, Suicidality and Self-harm	
Suicidality	
In the last 12 months have you thought about, made plans or attempted suicide?	
Yes	94 (17.1%)
No	456 (82.9%)
Self-harm	
During the last 12 months, have you deliberately hurt yourself or done anything you knew might have harmed you (but not kill you)?	
Yes – twice or more	64 (11.6%)

Yes – once	53 (9.6%)
No	433 (78.8%)
Depression symptoms[f]	Mean (SD)
Negativity towards looks	1.49 (0.64)
Irritability	1.46 (0.65)
Pessimism	1.33 (0.50)
Loneliness	1.25 (0.50)
Sadness	1.21 (0.45)
Self-criticism	1.20 (0.42)
Crying	1.17 (0.43)
Self-hatred	1.15 (0.39)
Feels unloved	1.13 (0.35)
Lack of friendship	1.13 (0.39)

[a]The sample after removal of those participants with more than 30% missing data for items on the psychometric inventories.

[b]The gender data used in this study were self-identified and collected in the 14-year wave as no gender data were collected in the 17-year wave. Participants were given the options of male, female or pass/don't know. The response of 'pass / don't know' was treated as missing data as cell counts for this response were very small.

[c] This group was made up of those who identified as Tokelauan, Niuean, or Fijian.

[d]This group was made up of those who identified as Pākehā (European New Zealanders), Māori or multiple Pacific groups equally.

[e]The level of socio-economic deprivation was assessed with a self-reported measure of food security, *Money for food.*

[f]The range for all depression symptom scores was from 1 to 3.

4.3.1. Distribution of Variables Conditioned on Suicidality

In the bivariate analyses, after adjusting for multiple testing, *Suicidality* was significantly associated with *Self-harm* (self-harmed once or more), *Gender* (female), *Smoke cigarettes* (yes), *Take drugs* (yes), *Part of school* (no); significantly lower mean scores for *Relationship with mother*, *Relationship with father*, *Relationship with friends*, and *GME (Group Membership and*

Belonging); and higher mean scores for *Negative peer pressure*, *Impulsivity*, and all depression symptoms. (see Appendix B Table B-3 for details of the associations between study variables with suicidality).

4.3.2. Network Estimation

In a network comprising depression symptoms, *Suicidality*, and *Self-harm*, Goldbricker identified *Self-harm* and *Suicidality* as too topologically similar and recommended the removal of *Self-harm*. However, as *Self-harm* was theoretically important to the study, depression symptom networks were fitted with and without *Self-harm*. When all other non-symptom variables were added to the network, Goldbricker detected *PCB* as too topologically similar to both *CE and GME*, and *Relationship with father* with *Relationship with mother*, but not *Self-harm* with *Suicidality*. Goldbricker recommended the removal of *PCB* and *Relationship with father*. To monitor the effect that removing *PCB* and *Relationship with father* would have on findings, networks were fitted with and without those variables. Therefore, in total, four networks were estimated:

- Network A – all depression symptoms and *Suicidality*
- Network B – all depression symptoms, *Self-harm,* and *Suicidality*
- Network C – all depression symptoms, *Self-harm*, *Suicidality*, and all other non-symptom variables except for *PCB* and *Relationship with father*
- Network D – all depression symptoms, *Self-harm*, *Suicidality*, and all other non-symptom variables

Details of node predictability can be found in Appendix B, Tables B-4 to B-7. Details of edge weights, inclusion probabilities, and bootstrap quantiles for the variables associated with *Suicidality* for all networks are reported in Table 11. See Appendix B for details of the weighted adjacency matrices for all networks (Tables B-8 to B-11)

In Network A, the strongest and most reliable association with *Suicidality* was *Pessimism* (w=0.30, Inclusion probability 99%, Bootstrapped 95% quantiles [0.12, 0.42]), followed by *Negativity towards looks* (w=0.19, Inclusion probability 94%, Bootstrapped 95% quantiles [0, 0.32]), *Sadness* (w=0.17, Inclusion probability 94%, Bootstrapped 95% quantiles [0, 0.32]), and *Loneliness* (w=0.12, Inclusion probability 80%, Bootstrapped 95% quantiles [0, 0.25]). These symptoms were positively associated with *Suicidality*, meaning they were potential risk indicators for *Suicidality*. *Suicidality* was directly associated with all other depression symptoms, except for *Self-criticism*, but with inclusion probabilities of less than 80%. *Suicidality* had a whole model predictability of 0.85 (intercept model = 0.83). See Figure 5 for the network graph.

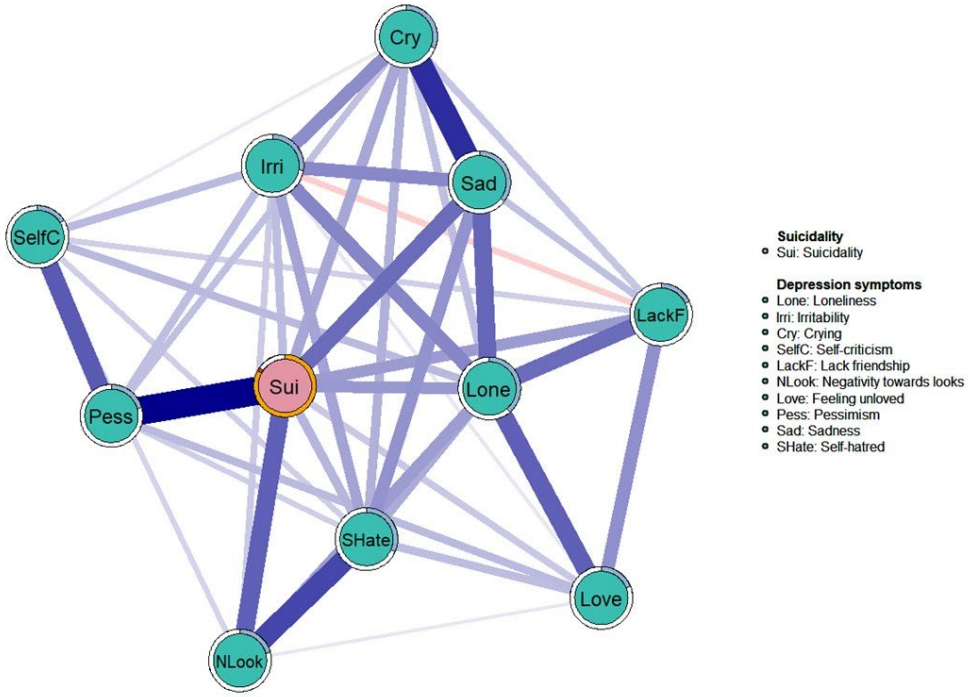

Figure 5 Network A, showing pairwise associations between depression symptoms and Suicidality, n=550

Wider and more colour-saturated edges depict stronger associations and the colour the nature of the association between two nodes: blue represents a positive association and red a negative association. The predictability of each node is shown by the shaded pie segment. This is light blue for continuous variables (depression symptoms) and displays the value of R-squared; and for the categorical variable (*Suicidality*), the yellow part of the segment represents the proportion of correct classification of the intercept model, the red part the improvement beyond this proportion attributable to neighbouring nodes, and the sum of both segments represents the proportion of correct classification of the whole model.

4.3.3. Network B (Depression symptoms, Self-harm, and Suicidality)

In Network B, the strongest and most reliable association with *Suicidality* was *Self-harm* (w=0.61, Inclusion probability100%; Bootstrapped 95% quantiles [0.41, 0.84]), followed by *Pessimism* (w=0.31, Inclusion probability 99%; Bootstrapped 95% quantiles [0.13, 0.46]). *Suicidality* was also associated with *Negativity towards looks*, *Sadness*, and *Irritability*, but with inclusion probabilities of less than 70%. All these symptoms were potential risk indicators for *Suicidality*. *Suicidality* had a whole model predictability of 0.86 (intercept model = 0.83). See Figure 6 for the network graph.

The odds of reporting *Suicidality* increased as incidences of *Self-harm* increased, with an odds ratio (OR) of 3.3 for those in level 2 of *Self-harm* (self-harmed once), rising to 5.8 for those in

level 3 (self-harmed twice or more), compared to the reference level (level 1) of no self-harming, all relevant to the last 12 months.

The strongest and most reliable associations with *Self-harm* (apart from *Suicidality*) were *Sadness* (w= 0.10, Inclusion probability 91%; Bootstrapped 95% quantiles [0, 0.26]), and *Negativity towards looks* (w= 0.10, Inclusion probability 87%; Bootstrapped 95% quantiles [0, 0.26]); and with *Pessimism* (apart from Suicidality) were *Self-criticism* (w= 0.19, Inclusion probability 99.5%; Bootstrapped 95% quantiles [0.11, 0.25]), and *Feeling unloved* (w= 0.08, Inclusion probability 81%; Bootstrapped 95% quantiles [0, 0.15]).

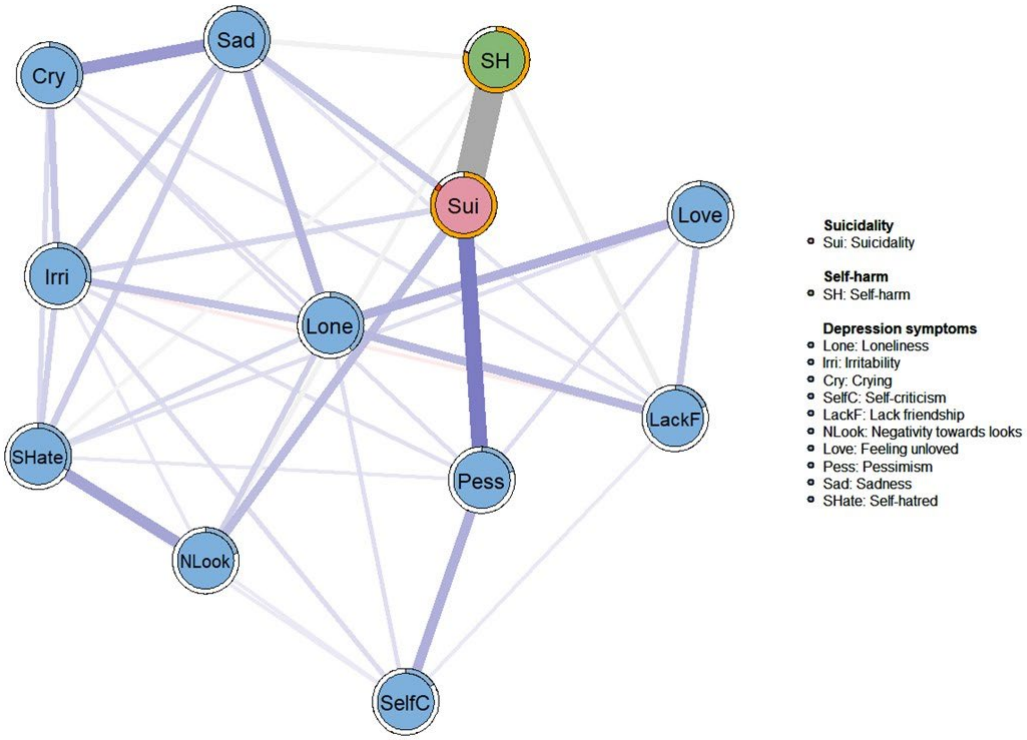

Figure 6 Network B, showing pairwise associations between depression symptoms, Self-harm, and Suicidality, n=550

Wider and more colour-saturated edges depict stronger associations and the colour the nature of the association between two nodes: blue represents a positive association, red a negative association, and grey means the nature of the association cannot be displayed in the network graph but is discoverable from post-hoc investigation. The predictability of each node is shown by the shaded pie segment. This is light blue for continuous variables (depression symptoms) and displays the value of R-squared; and for the categorical variables (*Suicidality* and *Self-harm*), the yellow part of the segment represents the proportion of correct classification of the intercept model, the red part the improvement beyond this proportion attributable to neighbouring nodes, and the sum of both segments represents the proportion of correct classification of the whole model.

4.3.4. Network C (Depression symptoms, Self-harm, other non-symptom variables (except relationship with father and PCB), and Suicidality)

In Network C, the strongest and most reliable association with *Suicidality* was *Self-harm* (w=0.51, Inclusion probability 100%, Bootstrapped 95% quantiles [0.36, 0.82]), followed by *Pessimism* (w=0.24, Inclusion probability 87%, Bootstrapped 95% quantiles [0, 0.41]). *Suicidality* was also positively associated with *Negativity towards looks, Sadness* and *Take drugs*; and negatively with *Relationship with mother* and *Part of school*, but these associations were much less reliable, with inclusion probabilities of 54% or less. Based on the results of the bootstrapped resamples, *Suicidality* was associated with *Hours online* and *Money for food*, with inclusion probabilities of 66% and 65%, respectively.

Suicidality had a whole model predictability of 0.87 (intercept model = 0.83). See Figure 7 for the network graph.

As with Network B, the OR for reporting *Suicidality* rose as incidences of *Self-harm* rose. It was 2.4, for those in level 2 of *Self-harm*, rising to 4.0 for those in level 3, compared to the reference level (level 1).

The strongest and most reliable associations with *Self-harm*, apart from *Suicidality*, were *Gender* (w= 0.19, Inclusion probability 94%; bootstrapped 95% quantiles [0, 0.47]); *Negative peer pressure* (w= 0.18, Inclusion probability 89%; bootstrapped 95% quantiles [0, 0.32]); and *Bullied online – victim* (w= 0.15, Inclusion probability 81%; bootstrapped 95% quantiles [0, 0.59]); and with *Pessimism* were *Self-criticism* (w= 0.17, Inclusion probability 99%; bootstrapped 95% quantiles [0.12, 0.26]) and *Binge drinking* (w= 0.12, Inclusion probability 87%; bootstrapped 95% quantiles [0, 0.27]).

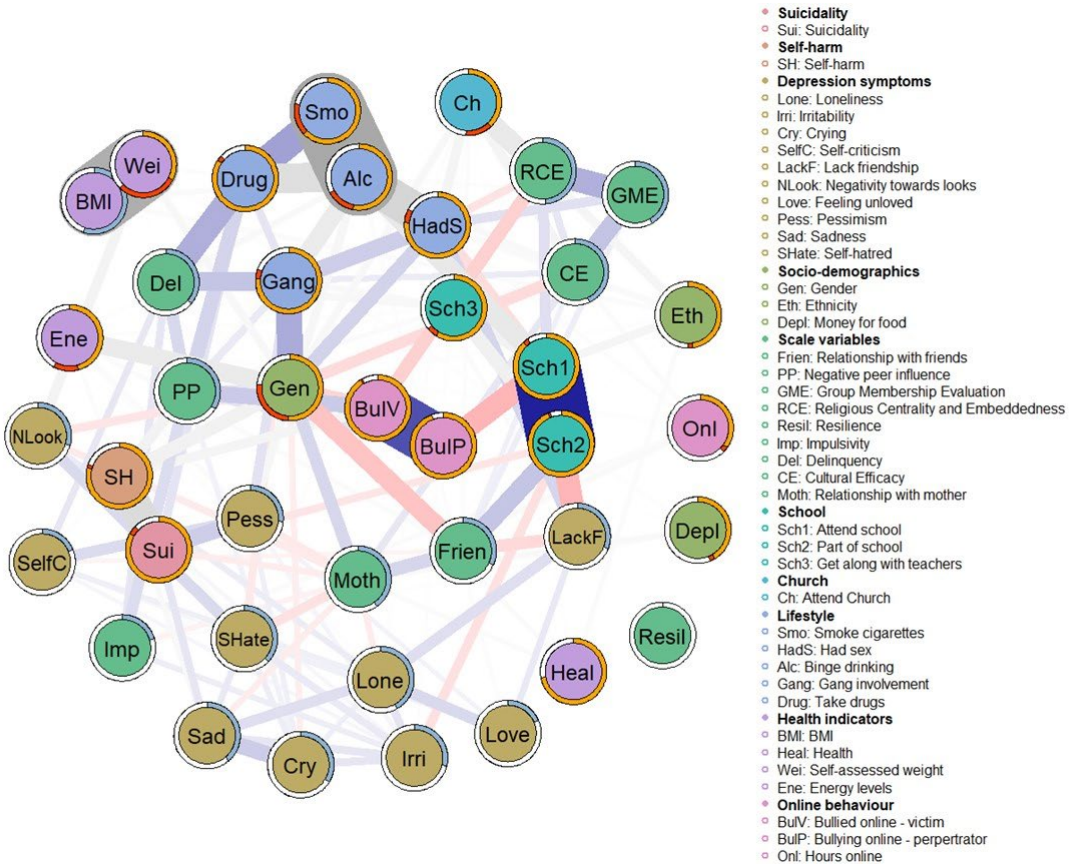

Figure 7 Network C showing the pairwise associations between depression symptoms, Self-harm, non-symptom variables (apart from Relationship with father and PCB), and Suicidality n=550.

Wider and more colour-saturated edges depict stronger associations and the colour the nature of the association between two nodes: blue represents a positive association, red a negative association, and grey means the nature of the association cannot be displayed in the network graph but is discoverable from post-hoc investigation. The predictability of each node is shown by the shaded pie segment. This is light blue for continuous variables and displays the value of R-squared; and for the categorical variables, the yellow part of the segment represents the proportion of correct classification of the intercept model, the red part the improvement beyond this proportion attributable to neighbouring nodes, and the sum of both segments represents the proportion of correct classification of the whole model.

4.3.5. Network D (Depression symptoms, Self-harm, all non-symptom variables, and Suicidality)

In Network D, the associations with *Suicidality* were identical to those in Network C, apart from very small changes in edge weights.

Table 11 Edge weights, inclusion probabilities, and bootstrapped 95% quantiles for pairwise associations with Suicidality

Network Index	Variables associated with Suicidality	Edge weight	Nature of association	Inclusion probabilities[c]	Bootstrapped 5%, 95% quantiles
Network A					
	Pessimism	0.30	+ve[b]	99%	0.12, 0.42
	Negativity towards looks	0.19	+ve	94%	0, 0.32
	Sadness	0.17	+ve	94%	0, 0.32
	Loneliness	0.12	+ve	80%	0, 0.25
	Lack of friendship	0.12	+ve	68%	0, 0.32
	Crying	0.10	+ve	73%	0, 0.24
	Self-hatred	0.09	+ve	62%	0, 0.24
	Irritability	0.08	+ve	58%	0, 0.22
	Feels unloved	0.06	+ve	61%	0, 0.23
Network B					
	Self-harm	0.61	na[b]	100%	0.41, 0.84
	Pessimism	0.31	+ve	99%	0.13, 0.46
	Negativity towards looks	0.16	+ve	68%	0, 0.29
	Sadness	0.14	+ve	61%	0, 0.29
	Irritability	0.10	+ve	54%	0, 0.24
Network C					
	Self-harm	0.51	na[b]	100%	0.36, 0.82
	Pessimism	0.24	+ve	87%	0, 0.41
	Take drugs	0.13	+ve	54%	0, 0.53
	Sadness	0.11	+ve	45%	0, 0.31
	Negativity towards looks	0.10	+ve	44%	0, 0.26
	Part of school	0.12	-ve	31%	-0.60, 0
	Relationship with mother	0.09	-ve	34%	-0.25, 0
	Hours online[a]	0	na[b]	66%	0, 0.27
	Money for food[a]	0	na[b]	65%	0, 0.30

[a]These edges were not present in the network but recovered in the bootstrap resamples.

[b]+ve means the relationship was positive, -ve that it was negative, and na that the sign for categorical variables with more than two levels cannot be shown visually in the network graph, but more information

about the nature of the association was extracted from post hoc testing (see section Network C (Depression symptoms, Self-harm, other non-symptom variables (except Relationship with father and PCB), and Suicidality)).

[c]Inclusion probabilities and bootstrapped quantiles were estimated with 200 resamples of the relevant network.

4.4. Discussion

The present study used network analysis to gain a deeper understanding of how individual depression symptoms and self-harm contributed to suicidality in a sample of Pacific NZ adolescents, whilst allowing for the impact of a range of other variables found to be associated with suicidality in previous research. Key results of the study were the differences in the contribution of individual depression symptoms to *Suicidality*, and the strength of the association with *Pessimism*. Other noteworthy findings were the consistent associations between *Suicidality* and *Negativity towards looks* and *Sadness*, and the differences in the non-symptom potential risk indicators for *Suicidality* compared to *Self-harm*.

Pessimism was the strongest and most reliable risk factor for *Suicidality*, other than *Self-harm*, across all networks. Pessimism, as measured by a single item on a depression inventory as in this study, has been found to be associated with adolescent suicide ideation in in two recent network analyses (Gijzen et al., 2021; Núñez et al., 2018). Of note was the association between suicide ideation and pessimism being weaker in the Gijzen et al. (2021) study compared to both the present study and the one by Núñez et al. (2018). Complementarily, optimism, as measured by Life Orientation Test-Revised (LOT-R; (Scheier et al., 1994)), has been found to be protective against suicidality (Yi et al., 2021).

In terms of clinical relevance, these findings suggest that negative expectations about the future should be regarded as an indicator of possible suicidality in Pacific adolescents in NZ. This could be vitally important in situations where adolescents may not feel able to admit to suicidal thoughts or behaviours but may feel more comfortable about reporting feeling pessimistic. Pessimism could also be a viable target for interventions. Focusing on the sources of pessimism and fostering optimism could help to reduce the severity or prevalence of suicidality and potentially suicide death amongst Pacific adolescents in NZ. Future research investigating the benefits of interventions aimed at reducing pessimism and promoting optimism, with the overall aim of alleviating suicidality, are warranted.

The symptoms *Sadness* and *Negativity towards looks* were the only other depression symptoms to be consistently associated with *Suicidality* across all networks, but these associations were typified by lower edge weights and reliability than for the association with *Pessimism*. It was not stipulated which aspects of looks were leading to this negativity. However, *Negativity towards looks* was strongly associated with *Self-assessed weight* and *Self-hatred* (see Figure 7), providing information about where the negative perceptions may be rooted and where interventions should focus attention. Other research has found dissatisfaction with body image to be a risk factor for self-harm (Gomez-Castillo et al., 2022; Tie et al., 2022), and suicide

ideation (Brausch & Muehlenkamp, 2007). Interventions that build self-esteem have been linked to more positivity around body image (O'Dea & Abraham, 2000). More research is needed to investigate how to mitigate these feelings of negativity towards one's appearance during adolescence, particularly against the backdrop of unrealistic body ideals constantly pushed on social media, which have an exacerbating effect (Gomez-Castillo et al., 2022; Marengo et al., 2018). Specific to Pacific adolescents in NZ, Teevale (2011) investigated whether a higher tolerance of a larger body size amongst Pacific adolescents was presenting an obesity risk, as has been suggested in relation to Afro-American women compared to their European counterparts (Kumanyika et al., 1993). Teevale (2011) found no support for this in their research, where obese and healthy weight students correctly perceived their weight status, and desired healthy body sizes. The present study supports these findings, with higher levels of self-assessed weight being associated with higher BMIs and those participants who self-reported being 'very overweight' having elevated symptom severity for *Negativity towards looks*. However, any attempt to tackle obesity amongst Pacific adolescents should be done in a socio-culturally specific manner, with reference to ethnic specific healthy weight ranges (Teevale, 2011).

Feeling sad goes to the root of the depressed state and is not an easy target for treatment, but if the severity of other symptoms associated with sadness could be alleviated then those feelings might abate.

The differential impact of individual depression symptoms on *Suicidality* supports the view, put forward in much psychological network literature, that analysing depression only in terms of a sum score of symptoms could obscure important information and hinder a fuller understanding of the mental disorder or problem being investigated (Fried & Nesse, 2015b; Fried et al., 2014). This was also illustrated in an earlier prospective study by Beck et al. (1985), where the pessimism item on the Beck Depression Inventory (BDI), as well as high scores on the Hopelessness Scale, predicted suicide deaths more accurately than depression sum scores, among a sample of patients hospitalized with suicide ideation (Beck et al., 1985). Where it is necessary to use depression sum scores, such as to gain a measure of overall symptom severity, analysis could be conducted additionally at the symptom-item level, to safeguard against a potential loss of critical information. Alternatively, multiple psychological scales could be used to measure the same construct, as suggested by Fried & Nesse (2015a). *Suicidality* was also associated with significantly higher severity scores for all depression symptoms in the bivariate analysis, as has been found elsewhere (Gijzen et al., 2021). These results also have implications for treating items in depression inventories related to suicidality as being equal with other symptom items, as occurs when items are summed to create a single variable. Future work could

investigate whether symptom items related to suicidality should be weighted, when included in sum scores, to gain a more accurate measure of depression severity.

Self-harm had the strongest and most reliable association with S*uicidality*, with the association strengthening for those who had self-harmed more than once, and these findings are consistent with the literature (Brunner et al., 2014; Coppersmith et al., 2017; Gillies et al., 2018). Teevale et al. (2016) found that over 70% of Pacific NZ adolescents who reported a suicide attempt, also reported self-harming. Self-harm and particularly repeated instances of self-harm have been found to be ominous predicters of suicide deaths (Hawton et al., 2020; Zahl & Hawton, 2004), although in these studies, no differentiation was made between self-harm with or without suicidal intent. There is debate as to whether self-harm and suicidal behaviours are discrete entities (Burešová, 2016; Cha et al., 2018; Coppersmith et al., 2017) or different dimensions of the same phenomenon (Hawton et al., 2012; Kapur et al., 2013). Dash et al. (2017) found that what constitutes self-harm has a cultural context, and Pacific understandings of self-harm, within the NZ environment, also included committing harm to the mental and spiritual self and gradual forms of self-harm, such as excess alcohol intake, as well as inflicting intentional harm to the physical self (Dash et al., 2017). Based on the findings of Dash et al. (2017) and the fact that the self-harm measure used was not tightly defined, *Self-harm* and *Suicidality* were treated as separate variables in this study. However, the extent to which the *Self-harm* and *Suicidality* were measuring the same construct statistically, based on the similarity of network associations, was tested using the goldbricker package (Jones, 2020). Goldbricker identified *Self-harm* and *Suicidality* as possibly measuring the same construct in the network of depression symptoms (Network A). However, the risk profiles of *Suicidality* and *Self-harm* differed fundamentally when non-symptom variables were added to the networks (Networks C and D). The strongest and most reliable potential risk indicators for *Self-harm*, other than *Suicidality*, were being female, being a victim of online bullying, and being susceptible to negative peer pressure. All of these factors have been found to be risk factors for suicidal thoughts or behaviours in other studies (Bilsen, 2018; Cha et al., 2018; Teevale et al., 2016), but they were not directly associated with *Suicidality* in this study, illustrating the complex interplay of factors involved in suicidality, which methods such as network analysis aim to capture. The results from goldbricker do not prove that *Self-harm* and *Suicidality* are separate constructs, but they do suggest that identifying potential risk factors for self-harm, separately to suicidality, could be a valuable component of suicide prevention strategies, particularly where what constitutes self-harm could be open to cultural interpretations, such as with Pacific people, who may be defining self-harm quite differently to established western norms.

Non-symptom potential risk indicators for *Suicidality*, apart from *Self-harm*, were *Take drugs, Money for food,* and *Hours online;* and protective factors were *Relationship with mother* and

Part of school. These potential risk indicators for *Suicidality* corroborate those in other studies (Cha et al., 2018; Consoli et al., 2013; Daniel et al., 2006; Kushal et al., 2021; Marchant et al., 2017; Rioux et al., 2021). Family and school environments have been found to be important factors for building resilience against suicide attempts amongst Pacific youth in NZ (Teevale et al., 2016), and also protective against depression (Gossage et al., 2022). The collectivist nature of Pacific culture (Podsiadlowski & Fox, 2011) could be in part responsible for the importance of family and social relationships for good mental health for Pacific youth. These results provide support for involving family and school in treatment plans and prevention strategies for Pacific adolescents in NZ (Teevale et al., 2016), although the ability to build quality relationships could be a proxy for other factors, such as personality structure, schemas, and adaptiveness (Roelofs et al., 2011).

In this sample, the prevalence of 12-month suicide ideation (16%) and suicide attempts (5.5%) was higher than the average rates from a recent meta-analysis of adolescent samples from other countries (12-month suicide ideation: 14.2%; suicide attempt (4.5%) (Lim et al., 2019).

4.5. Limitations

A strength of this study was that as the sample was from a birth cohort, it is likely to be broadly representative of the selected population. One of the main limitations was its cross-sectional design, meaning causality could not be established. The study also did not test for moderators, and some variables, such as those measuring personality and schema, might have robust moderating effects in this model, which could be investigated in future research. It made no distinction between those adolescents who ideated, planned, or attempted suicide, due to small cell counts for those who planned or attempted suicide. Only a small fraction of those with suicide ideation will attempt suicide, and the characteristics of those who have ideated suicide compared to those who have attempted suicide has been shown to differ (Goldston, 2004; Kuroki, 2015). Future research could investigate these differences through longitudinal trajectories of suicide risk for Pacific adolescents and young adults to identify points of intervention that would reduce the risk of suicide ideation leading to suicide attempt and suicide death. The role of self-harm in this trajectory should also be investigated. The sample was representative in terms of national proportions of Pacific NZ youth, aged 15-19, for gender and in terms of Samoan and Tongan ethnic groups, however, those identifying as Cook Islands Māori or Other Pacific Island were underrepresented in this sample (Statistics NZ, 2018). The community sample was relatively homogeneous in terms of age, socio-economic status, and ethnicity, so findings may not generalize to other populations or clinical samples. Although the sample was relatively homogeneous, individuals within it will differ, so the findings are most relevant in terms of providing insight at the group level, rather than at the individual level. Not

all known predictors of suicidality were able to be included, such as those measuring sexual and gender identity.

4.6. Conclusions

In this sample of Pacific adolescents in NZ, the largest contributors to *Suicidality* were *Pessimism* and *Self-harm*. Overall, the risks that individual depression symptoms presented for *Suicidality* varied enormously, supporting the view that analysing psychopathological problems at the symptom-item level provides an in-depth insight that can valuably inform treatment approaches (Fried & Nesse, 2015a; Fried et al., 2014; McNally, 2016). Measuring depression in terms of a single construct is still necessary for diagnostic and clinical trial purposes, but supplementing this with symptom level analysis, provides additional information that could complement case formulation and individualised treatment strategies (MacNeil et al., 2012). The strongest and most reliable association with *Suicidality* was *Self-harm*, but the non-symptom potential risk indicators for *Self-harm* and *Suicidality* were fundamentally different. Screening for self-harm in psychological assessments, separate to suicidality, could be an important aspect of suicide prevention for Pacific adolescents in NZ.

Prelude to Chapter 5

This was a literature review of published research investigating associations between the three most studied inflammatory biomarkers (CRP, IL-6, and TNF-a) with depression dimensions, subtypes, and individual depression symptoms. The results of this literature review were used to inform the hypotheses in Chapter 6.

Chapter 5. Literature Review: Associations between Inflammatory Markers and Depression Dimensions, Subtypes and Symptoms

5.1. Depression Prevalence

Depression is one of the most common mental disorders and more than 300 million are affected by it worldwide, around 4.4% of the world's population, and the burden of depression and other mental health conditions is on the rise globally (WHO, 2018). It accounts for the largest burden of non-fatal disease in the world, due to its high prevalence, the associated disability that can accompany it and the young age at which it can start in many cases (Ustun et al., 2004). Additionally, having major depression increases one's risks of mortality through its comorbidity with other diseases such as cardiovascular disease (Wulsin et al., 2009). However, despite its prevalence it remains an elusive disease. It is difficult to diagnose and treat. A study found that only around half of those suffering from Major Depressive Disorder (MDD) receive a diagnosis of it through general practice (van Rijswijk et al., 2009). It is thought that major contributing factors in effectively diagnosing and treating depression are its highly heterogeneous nature in terms of symptom presentation and its comorbidity and overlapping symptoms with other psychological disorders, such as substance use disorder (Rohde et al., 2018), and somatic symptom overlap with illness and chronic diseases (Gold et al., 2020), which can make it hard to distinguish it from these other disorders and medical conditions.

5.2. Inflammation and Depression

The burden of depression on individuals and society as a whole, the difficulty in diagnosing and treating it have led to practitioners, academics, researchers and others working in mental health to seek biomarkers that could help identify that someone is depressed and enable treatments to be targeted at them with more scientific precision This search for biomarkers for depression has led to inflammation, specifically low-grade, chronic inflammation, being implicated as a significant contributor to the pathophysiology of major depression, and the development of the cytokine theory of depression (Berk et al., 2013; Maes, 1995; Raison et al., 2006; Raison & Miller, 2011). According to this theory, pro-inflammatory cytokines are released in response to physical or psychological stressors, and these pro-inflammatory cytokines can cross the blood brain barrier and disrupt biological pathways that are involved in mood regulation and contribute to the development and progression of depression (Maes et al., 2012; Raison et al., 2006; Raison & Miller, 2011).

There now exists a significant body of work supporting a link between at least one inflammatory biomarker, such as IL-6, TNF-a, or CRP, and depression, including a number of large meta-analyses (Bizik, 2010; Dowlati et al., 2010; Hiles et al., 2012; Horn et al., 2018; Howren et al., 2009; Kohler et al., 2017; Osimo et al., 2019). These studies make strong cases for the existence of an association independent of other confounding factors, such as cardiovascular risk. Some meta-analyses have also focused on the direction of the relationship and have found evidence that elevated inflammatory cytokines can predict depression (Valkanova et al., 2013) . However, inconsistencies still abound in studies covering this topic and the reasons for these inconsistencies are still dynamic areas of ongoing research. Although a large number of studies (cross sectional, longitudinal and meta-analytic) do show significant associations, a large number also do not (e.g. Euteneuer et al., 2017a; Köhler-Forsberg et al., 2017; Jesper Krogh et al., 2014; Steptoe et al., 2003) or show that the association disappears after covariate adjustment (de Menezes et al., 2017; Duivis et al., 2013; Gialluisi et al., 2020). Negative correlations between inflammation and depression have also been found (Schmidt et al., 2016).

Furthermore, amongst the meta-analyses that have found significant associations between inflammatory markers and depression, effect sizes have been found to vary substantially and commonly there was significant heterogeneity between studies included in the meta-analyses (Bizik, 2010; Dowlati et al., 2010; Hiles et al., 2012; Howren et al., 2009; Kohler et al., 2017), which was only partly explained by subgroup analysis. The study by Kohler et al. (2017), for example, found that the proportion of smokers in the sample moderated effect sizes, with a higher proportion being associated with a larger effect size. Most metanalyses have only included studies with clinically depressed samples, but among two that included community as well as clinical samples, effect sizes were much smaller for the community samples compared to clinical, although still significant (Hiles et al., 2012; Howren et al., 2009).

Controlling for certain covariates has also had a large attenuating impact on effect sizes, particularly BMI (Horn et al., 2018; Howren et al., 2009). Horn et al. (2018) found in a meta-analysis investigating associations between depression and CRP that the effect size was very small after controlling for age, sex, obsesity, medical conditions, substance use, medication, and psycho-social factors. Furthermore, in subgroup analysis, filtering on study quality, when only the studies with the highest level of methodological rigour were included the effect size became non-significant (Horn et al., 2018). A number of studies have found that the association between depression and at least one inflammatory marker became non-significant after adjusting for covariates, particularly markers of an unhealthy lifetsyle, such as BMI, alcohol consumption, smoking, and physical inactivity (de Menezes et al., 2017; Duivis et al., 2013; Gialluisi et al., 2020; Kop et al., 2002; Michal et al., 2013), leading some researchers to claim that it is the

confounding effects of these factors, being associated with both depression and inflammation, that is driving the association (e.g. Duivis et al., 2013; de Menezes et al., 2017).

The inconsistencies across studies investigating the nature of the inflammation and depression relationship suggest that not all depressed people are inflamed. However, it is generally accepted that certain subgroups of depressed people also exhibit raised levels of some inflammatory markers (Berk et al., 2013; Raison et al., 2006; Raison & Miller, 2011), estimated at between 25-30% of depressed subjects (Osimo et al., 2019), but what characterizes this group is still an area of ongoing research. Those depressed people who are also inflamed, are also more likely to suffer from difficult to treat depression, so gaining further understanding of what typifies them is particularly important (Strawbridge et al., 2019; Suneson et al., 2023). There is much variability in the symptom presentation amongst depressed people (Fried & Ness, 2015b; Monroe & Anderson, 2015), and it is argued that this variability could be holding back progress in terms of identifying reliable biomarkers (Fried & Cramer, 2017; Penninx et al., 2013). There is evidence that the nature of the inflammation-depression relationship differs depending on depression dimensions, subtypes, symptom clusters, or even individual symptoms of depression and it is the heterogeneity of symptom presentation that is leading to inconsistent and sometimes conflicting results. The objective of this literature review was to appraise the published evidence for associations between inflammatory markers with certain depression dimensions, depression subtypes, and individual symptoms, and assess whether associations with certain inflammatory markers are more likely depending on depression subtypes and symptom profiles and whether inflammatory markers are differentially associated.

5.2.1. Inflammation and Depression Dimensions

5.2.1.1. Inflammation and Somatic Depression

Somatic depression symptoms are those with physical manifestations, and although there is not a standardised definition of somatic depression, subscales measuring this dimension consistently include symptoms related to fatigue, appetite changes, and sleep changes. Most of the theoretical and empirical research into associations between inflammation and depression at the dimension level emphasise associations with somatic symptoms, and an influential theory in this area is Sickness Behaviour Theory (Dantzer, 2006; Dantzer & Kelley, 2007; Raison et al., 2006; Raison & Miller, 2011). According to Sickness Behaviour Theory, depression symptoms (such as loss of appetite, sleepiness, and fatigue) that overlap with symptoms of sickness or infection, are the result of upregulated inflammation (Dantzer, 2006; Dantzer & Kelley, 2007). When the body is fighting an infection it produces upregulated cytokines, such as IL-6 or TNF-a, and these cytokines trigger sickness behaviours as a way of conserving energy and fighting infection. However, this response can become maladaptive and chronic and lead to the

activation of those depression symptoms which are also the body's normal response to illness and infection (Dantzer et al, 2008).

Another related theory linking inflammation and somatic depression is that it is the confounding effects of factors associated with an unhealthy lifestyle, such as high BMI, substance use, poor diet and physical inactivity that are driving this link (Duivis et al. 2013; de Menezes et al., 2017), with inflammation as a possible mediating pathway that increases both the risk and progression of depression (Berk et al., 2013). Lifestyle factors are likely to influence somatic symptoms more than psychological, as the results of factors such as obsesity, smoking, alcohol consumption, and sedentary behaviour, are more likely to be felt physically, such as associations between poor diet with fatigue, lack of exercise with sleep disturbances, and physical aches and pains with substance abuse.

5.2.1.2. Inflammation and Psychological Depression

As with somatic depression dimension, there is not an established symptom list for this depression dimension, but the symptoms typically associated with psychological depression often include sadness, pessimism, loss of pleasure, self-criticalness, and suicidal thoughts. It is argued that when inflammation passes the blood brain barrier, it is likely to affect emotional and cognitive functioning and so impact symptoms on the psychological depression subscale (Leonard & Maes, 2012; Maes, 1995). There are also theories that link psychological depression symptoms with inflammation, through the links between psychological depression and anhedonia via its ability to disrupt reward processing pathways in the brain (Felger, 2017; Felger & Miller, 2012).

5.2.2. Inflammation with Depression Subtypes

5.2.2.1. Inflammation with Atypical Depression

As with somatic depression dimension, atypical depression is more defined by physical symptoms, but in contrast to somatic depression the direction of the disturbances related to appetite and sleep (increased and decreased) are defined. According to the DSM-V manual (American Psychiatric Association, 2013), a diagnosis of atypical depression must include mood reactivity (brightens in response to positive events), plus two or more of the following: increased appetite (hyperphagia) or weight, increased sleep (hypersomnia), leaden paralysis (as would be experienced with severe fatigue), or interpersonal rejection sensitivity. However, research has shown that atypical depression is largely defined by increased appetite or weight, hypersomnia, and fatigue / energy related symptoms and there have been calls to drop the mandatory 'mood reactivity' from the list (Silverstein & Angst, 2015), with appetite / weight being the symptom best able to discriminant between subtypes (Lamers et al., 2010).

One theory linking inflammation with atypical depression is that it is metabolic dysregulation that is underlying the association. The symptom profile in atypical depression is thought to be associated with metabolic syndrome components, such as obsesity and insulin resistance, which leads to a pro-inflammatory state and it is the associations between metabolic syndrome components, certain depression symptoms and inflammation that is driving the link between depression and inflammation (Lamers et al., 2018; Milaneschi et al., 2020; Simmons et al., 2020).

5.2.2.2. Inflammation and Melancholic Depression

Symptoms of melancholic depression include loss of pleasure, depressed mood, decreased appetite, and insomnia. As with the theories linking psychological depression with inflammation, it is proposed that neuroinflammation may impact mood and cognitive function, which is in line with the cytokine theory of depression (Raison et al., 2006; Raison & Miller, 2011). Another theory more specific to melancholic depression is that over activation of the hypothalamic-pituitary-adrenal (HPA) axis can result in elevated cortisol levels, which may trigger or worsen symptoms of melancholic depression (Lamers et al., 2013).

5.2.3. Inflammation with Individual Depression Symptoms

Early proponents of the cytokine theory of depression noted that certain symptoms, such as those relating to sleep disturbance and other sickness behaviour symptoms, could be driving the relationship between inflammation and depression (Capuron & Miller, 2004; Dantzer, 2006), Dantzer and Kelley (2007) investigated how pro-inflammatory cytokines can alter signalling pathways to induce sickness behaviour, which can lead to symptoms like loss of appetite and fatigue. Research by Lamers et al. (2013) found different biological correlates with the depression subtypes of atypical and melancholic depression, which were largely dependent on the nature of appetite changes, increased or decreased (Lamers et al., 2013). However, most research empirically investigating associations with inflammatory markers at the symptom item level has occurred within the last 10 years and one of the earliest studies comprehensively investigating associations between inflammation with a wide range of depression symptoms was Jokela et al. (2016).

5.3. Methodology

This review investigated associations between depression dimensions, subtypes, and individual depression symptoms with the inflammatory biomarkers CRP, IL-6, and TNF-a. These inflammatory biomarkers were chosen as they are the most commonly studied. The objective was to assess whether associations between biomarkers were more likely for certain depression dimensions, subtypes, and individual symptoms. The depression dimensions the review focused on were somatic (also referred to neurovegetative in many studies reviewed and both terms used

interchangeably in this review) and psychological (also referred to as cognitive in many studies and both terms used interchangeably in this review). These terms were used interchangeably as there are no standard definitions of what symptoms should be included in these dimensions, but generally there is a lot of overlap between the symptoms included in somatic and neurovegetative depression dimension and between those included in psychological and cognitive or depressed mood. Where depressed mood was included as a depression dimension, it was classed as psychological. The main depression subtypes studied were atypical and melancholic or non-atypical.

The database used was PubMed, which was searched for suitable studies between August 2024 and October 2024. Studies were identified using combinations of the following terms: depres*, "symptom dimension*", "somatic", "neurovegetative", "cognitive", "psychological", "atypical"; "melanchol*", "individual symptom", "CRP", "IL-6", "TNFa", "C reactive protein", "interleukin 6", "tumour necrosis factor" and "tumor necrosis factor". The search turned up a number of systematic reviews which were also checked for relevant studies and where appropriate individual studies from these reviews were then included. Inclusion criteria included cross-sectional study design, depression measured in terms of somatic or psychological subscales (or included at least one of these subscales), or depression subtypes atypical or melancholic or non-atypical (or included at least one of these subtypes), or as individual depression symptoms. Other inclusion criteria were that the population studied, or samples used were free of major medical conditions or mental disorders other than depression, and which included at least one of the inflammatory markers of interest. Studies where inflammation was stimulated were also excluded. In total, the search identified 47 relevant studies.

5.4. Results

5.4.1. Evidence for an Association between Inflammatory Markers and Somatic Depression

5.4.1.1. Somatic Depression Dimension with CRP

Fifteen studies were identified that investigated associations between CRP and somatic depression. Out of these, seven studies found CRP positively associated with somatic symptoms after adjustment for covariates (Case & Stewart, 2014; Elovainio et al., 2009; Foley et al., 2021; Iob et al., 2020; Jokela et al., 2016; Straka et al., 2020; White et al., 2017), three were significantly associated pre full-adjustment, but were no longer significant after adjusting for variables associated with an unhealthy lifestyle, such as smoking and BMI (Duivis et al., 2013; Michal et al., 2013; Milaneschi et al. 2021), and five had null findings (Bremmer et al., 2008; Dannehl et al., 2014b; Euteneuer et al., 2017; Köhler-Forsberg et al., 2017; J. Krogh et al., 2014). In the study by Case and Stewart (2014), a study in the United States, there was evidence of moderation by race/ ethnicity. Amongst non-Hispanic White participants, the association was

same as for the full sample, raised CRP with somatic depressive symptoms, but for non-Hispanic Black, Mexican American or Other Hispanic groups there were no associations between CRP with somatic depressive symptoms (or with psychological or total depressive symptoms) (Case & Stewart, 2014). The study by Elovainio et al. (2009) there was evidence of moderation by gender as higher CRP was associated with somatic symptoms only in men after adjustment; in women this association became non-significant after controlling for covariates.

5.4.1.2. Somatic Depression Dimension with IL-6

Ten studies were found that investigated associations between IL-6 and somatic depression dimension. One found a positive association between IL-6 with somatic depression pre and post adjustment (Straka et al., 2020), but in this study they also found that age moderated the relationship and after conducting age stratified analysis, IL-6 was not associated with somatic depression symptoms for those aged under 41. Three found a positive association pre full adjustment but this became non-significant after the inclusion of all covariates. For two of the three, this occurred only after adjusting for markers of an unhealthy lifestyle (such as BMI and smoking) (Duivis et al., 2013; Milaneschi et al., 2021). For the third, the significant relationship remained after adjusting for age, income, and race/ ethnicity, but became non-significant after adjusting for inflammatory diet scores (Hazeltine et al. (2022). Six found no significant associations with somatic depression symptoms (Bremmer et al., 2008; Dannehl et al., 2014; Euteneuer et al., 2017; Krogh et al., 2014; Peters et al., 2021; Sica de Rocha, 2020).

In the six studies that examined associations between TNF-a with somatic depression, one found a positive association pe and post adjustment (Peters et al., 2021), two found positive associations pre full adjustment. For one, the association became non-significant after adjusting for variables associated with an unhealthy lifetsyle (Duivis et al., 2013), and for the other the significant relationship became non-significant after adjusting for inflammatory diet scores (Hazeltine et al., 2022). Two found no cross-sectional associations between TNF-a and somatic symptoms (Dannehl et al., 2014; Sica da Rocha, 2020), and one found a negative association between TNF-a with somatic symptoms (Schmidt et al., 2016). Dannehl et al. (2014) did find, however, that higher somatic symptoms in women predicted increased TNF-a over four weeks.

5.4.2. Evidence for an Association between Inflammatory Markers and Psychological Depression

5.4.2.1. Psychological Depression with CRP

Fourteen studies examined links with psychological depression dimension. Two found associations between higher CRP with psychological depression. Köhler-Forsberg et al. (2017) found associations between CRP with psychological depression symptoms, but only in women, and no associations with somatic depression symptoms. Interestingly, for the somatic symptom dimension, this study only included decreased appetite and insomnia (Köhler-Forsberg et al.,

2017). Iob et al. (2020) found raised CRP associated with both somatic and psychological depression symptoms, but the association was much weaker for psychological. Straka et al. (2021) found CRP was negatively associated with anhedonia. In the studies by Jokela et al. (2016), Case and Stewart (2014), and White et al. (2017), there were also significant associations between higher CRP with psychological depression symptoms, but these associations became non-significant after controlling for somatic depression symptoms. In two other studies, the significant association became non-significant after adjusting for covariates. In Duivis et al. (2013), this occurred after the first level of adjustment, which involved adjusting for socio-demographic variables; and in Elovainio et al. (2009), this association was only found in men but became non-significant after adjusting for all covariates. Foley et al. (2021) only examined links between somatic and overall depression severity and found that higher CRP was associated with total depression scores. The other studies did not find any cross-sectional links between CRP with psychological depression (Bremmer et al., 2008; Euteneuer et al., 2017; Krogh et al., 2014; Michal et al., 2013; Milaneschi et al., 2021; Schmidt et al., 2016).

5.4.2.2. Psychological Depression with IL-6

Ten studies investigated associations between IL-6 with psychological depression, and two found positive associations. Specifically, Peters et al. (2021) found higher IL-6 associated depressed mood and Straka et al. (2020) raised IL-6 with more interpersonal problems (both more linked to the psychological depression domain). Straka et al. (2020) also found higher IL-6 associated with less anhedonia. In one study, the association became non-significant after adjusting for socio-demographic covariates (Duivis et al., 2013). Sica de Rocha (2020) investigated associations between IL-6 with six melancholic domains, including a somatic domain (although it is not stated what symptoms were included in each domain), but the only association was with the most severe melancholic group, characterised by psychomotor retardation. There were no associations found in the other six studies (Bremmer et al., 2008; Dannehl et al., 2014; Euteneuer et al., 2017; Hazeltine et al., 2022; Krogh et al., 2014; Milaneschi et al., 2021).

5.4.2.3. Psychological Depression with TNF-a

Six studies examined associations between psychological depression with TNF-a and one found a negative association (Schmidt et al., 2018), in another, the association became non-significant after adjusting for socio-demographic covariates (Duivis et al., 2013); and four found no associations between TNF-a with psychological depression (Dannehl et al., 2014; Hazeltine et al., 2022; Peters et al., 2021; Sica de Rocha).

5.4.3. Evidence of an Association between Inflammatory Markers with Atypical Depression or Melancholic Depression

5.4.3.1. CRP with Atypical Depression or Melancholic

Eleven studies examined the relationships between CRP with atypical and melancholic (or non-atypical) or depressed groups with those features of atypical and melancholic, and one study used a measure for inflammation based on CRP and IL-6 combined. In five studies, levels of CRP were higher in atypical depression group compared to melancholic depression or healthy controls, (Badini et al., 2022; Hickman et al., 2014; Lamers et al., 2013; Moilanen et al., 2024; Simmons et al., 2020). Badini et al. (2022) found that the group with atypical features (weight gain and hypersomnia) had higher polygenic risk scores for CRP (CRP PRS) but the group with melancholic features (weight loss and insomnia) did not. Simmons et al. (2020) found raised CRP in the depressed group characterised by increased appetite, but not in the depressed group with decreased appetite. Moilanen et al. (2024) found elevated CRP amongst those with both atypical depression and melancholic compared to non-depressed, but the association was stronger for the atypical depression group. Brydges et al. (2022) used an immuno-metabolic dimension (IMD) constructed from summing symptoms for hypersomnia, increased appetite, increased weight, low energy, and leaden paralysis and found it was positively associated with an inflammatory index (a composite measure of CRP and IL-6).

In two other studies, CRP was associated with atypical depression pre-adjustment, but not after (Glaus et al., 2014; Liu et al., (2022). However, in the study by Liu et al. (2022), this was only just outside significance (P= 0.06). Karlovic et al., 2012 found that CRP was negatively associated in the atypical depression group (Karlovic et al., 2012), and another study found CRP in the atypical depression group (termed non-melancholic in this study) was significantly lower than controls (Rothermundt et al., 2001). However, Karlovic et al. (2012) found higher CRP was linked with duration of the disorder in the atypical group. One study used an older subsample (60 or over) of the cohort used by Lamers et al. (2013), but in contrast with Lamers et al. (2013), found no significant differences in the CRP levels between depressive subtypes and concluded this was probably due to the confounding effects of aging (Veltman et al., 2018).

5.4.3.2. IL-6 with Atypical Depression or Melancholic

Ten studies examined associations between IL-6 with atypical and melancholic depression. Out of these three found IL-6 levels to be higher in melancholic depressed group compared to controls, but no differences between IL-6 levels for controls and atypical depression group (Dunjic-Kostic et al., 2013; Karlovic et al., 2012; Spanemberg et al., 2014). Contrastingly, two studies found higher levels of IL-6 for the atypical group compared to melancholic and controls (Lamers et al., 2013; Rudolf et al., 2014), and a third found a raised inflammatory index in the atypical group based on a composite measure of IL-6 with CRP (Brydges et al., 2022). Four

studies found no significant associations between IL-6 with atypical or melancholic depression groups (Glaus et al., 2014; Liu et al., 2022; Veltman et al., 2018; Yoon et al., 2012), but Glaus et al. (2014) did find lower IL-6 associated with combined melancholic-atypical for those in this group with a lifetime diagnosis and for those in the unspecified depression subgroup group.

5.4.3.3. TNF-a with Atypical Depression or Melancholic

Of the six studies reviewed, which analysed the relationships between TNF-a with melancholic and atypical depression, one found that TNF-a was significantly higher amongst those with melancholic depression compared to the other subgroups (treatment resistant depression, chronic depression, and depression with chronic fatigue), but this study did not measure atypical depression (Maes et al., 2012). Another study found that TNF-a was significantly higher in atypical compared to melancholic depression and remained significantly higher after adjustment (Lamers et al., 2013). In contrast, Dunjic-Kostic et al. (2013) found that TNF-a levels to be significantly lower amongst those with atypical depression compared to controls. The three other studies found no significant associations between TNF-a with either depression subtype (Glaus et al., 2014; 2012; Liu et al., 2022; Yoon et al., 2012), but Glaus et al. (2014) did find lower TNF-a associated with combined melancholic-atypical subtype for those in this group with a lifetime diagnosis and for those in the unspecified depression subgroup group.

5.4.4. Evidence of an Association between Inflammatory Markers with Individual Depression Symptoms

5.4.4.1. CRP with Individual Depression Symptoms

Thirteen studies were reviewed that examined associations between individual depression symptoms with CRP (Chae et al., 2022; Foley et al., 2021; Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016; Kappelmann et al., 2021; Köhler-Forsberg et al., 2017; Lee et al., 2023; Manfro et al., 2022; Milaneschi et al., 2021; Moriarity et al., 2021; Sharpley et al., 2019; Shell et al., 2022), plus one that used an inflammatory index based on CRP, IL-6, and TNF-a (van Eeden et al., 2020). Jokela et al. (2016) found that the symptoms sleep problems, tiredness/ lack of energy, and changes in appetite, all somatic symptoms, were all independently associated with higher CRP. An independent association between higher CRP with anhedonia was very close to significance (Jokela et al., 2016). Köhler-Forsberg et al. (2017) found higher CRP with loss of interest and activity (a construct that maps to anhedonia) and suicidality in women but not men. In a pooled analysis of 15 population-based cohort studies, after covariate adjustment the most consistent associations with higher CRP were changes in appetite, everything an effort, loss of energy, and sleep problems and little interest in doing things (a construct aligned with anhedonia) (Frank et al., 2021). In this study, there was no or very little evidence of any associations with four emotional symptoms (bothered by things, hopelessness, felt fearful, and life had been a failure) (Frank et al., 2021). Fried et al. (2020), in a procedural replication of the

study by Jokela et al. (2016), found that raised CRP was associated with sleep problems and energy levels, after adjustment, and in a full model which included 28 symptoms, with trouble falling asleep, sleep too much, aches and pains and irritability. Two other studies found CRP was positively associated with appetite disturbance (Lee et al., 2023; Moriarity et al., 2021), and in one also with loss of energy (Moriarity et al., 2021). Kappelmann et al. (2021), in a study combining three samples and calculating the biomarker data using polygenic risk scores (PRS), found that higher CRP PRS was robustly associated with appetite changes. Milaneschi et al. (2021) in a study combining data from the UK and Netherlands, found higher CRP was associated with depression symptoms of depressed mood, altered appetite, sleep problems, and fatigue.

Most studies measured appetite as a compound symptom (with disturbances related to increased and deceased appetite combined into symptom), but some did measure it as disaggregated into increased and / or decreased changes in appetite. Milaneschi et al. (2021), in the study combining data from the UK and Netherlands, found increased appetite was associated with CRP in the Netherlands sample (the UK sample did not disaggregate symptoms related to appetite), but the association was no longer significant after adjusting for BMI. CRP was also associated with hypersomnia (Milaneschi et al., 2021). Chae et al. (2022) also found association between CRP with increased appetite, but this also no longer significant after adjustment for BMI and other metabolic syndrome components. Another study with young adults detected associations between CRP with anhedonia, fatigue, and weight loss (this study did not measure increased appetite or weight) (Manfro et al., 2022). Sharpley et al. (2019) found depression related fatigue was related to the ratio of cortisol to CRP but discovered this was being driven by higher CRP levels rather than cortisol. Foley et al. (2021) discovered associations for higher CRP with the somatic symptom of concentration difficulties and the psychological symptoms of feeling guilty, pessimism and indecisiveness after covariate adjustment, but these associations became non-significant controlling for false discovery rate (FDR). Shell et al. (2022) found that a somatic symptom cluster characterised by increased appetite, hypersomnia, and insulin resistance, and with CRP partly mediating the associations between hypersomnia and insulin and BMI partly mediating all relationships in the cluster. Race/ ethnicity moderated these associations, however, as the link between appetite and insulin resistance was positive for White participants and negative for Black participants (Shell et al., 2022).

5.4.4.2. IL-6 with Individual Depression Symptoms

Five studies were reviewed that analysed IL-6 with individual depression symptoms (Fried et al., 2020; Kappelmann et al., 2021; Manfro et al., 2022; Milaneschi et al., 2021; Motivala et al., 2005). Fried et al. (2020) found IL-6 positively associated with trouble falling asleep, sleep too

much, aches and pains and negatively with irritability. Two studies found IL-6 was positively associated with poor appetite, when the symptom was disaggregated (Milaneschi et al., 2021; Manfro et al., 2022. In fact, Milaneschi et al. (2021) found divergent associations with appetite, with elevated CRP associated with increased and elevated IL-6 with decreased. Milaneschi et al. (2021) also found associations between raised IL-6 with appetite change, sleep problems and fatigue in the analysis which combined the two samples (one from the UK and one from the Netherlands), and in the Netherlands sample, higher IL-6 with anhedonia and increased sleep, as well as decreased appetite. Manfro et al. (2022) found associations between IL-6 with restless sleep, depressed mood and worthlessness (as well as decreased appetite), and Frank et al. (2021) detected an association between IL-6 also with worthlessness. Kappelmann et al. (2021), in a combined study with 3 large samples, found no robust associations between IL-6 PRS with depression symptoms.

5.4.4.3. TNF-a with Individual Depression Symptoms

Two studies were reviewed that analysed TNF-a with individual depression symptoms. Kappelmann et al. (2021) discovered a robust association between TNF-a PRS with fatigue and Fried et al. (2020) detected positive associations between TNF-a with trouble falling asleep, sleep too much, aches and pains and irritability.

5.4.4.4. Inflammatory Index with Individual Depression Symptoms

In a study examining associations between the 30 items on the Inventory of Depression Symptoms (IDS) with an inflammatory index based on transformed mean levels of CRP, IL-6, and TNF-a, 20 symptoms were found to be associated with inflammation, after adjusting for multiple testing (van Eeden et al., 2020), and of these 14 were somatic symptoms and 6 non-somatic (or non-sickness behaviour related, as per the authors). The symptoms most strongly associated (that is P-values <0.001) were sleeping too much, increased appetite, decreased weight, pessimism, general interest, energy levels, capacity for pleasure, interest in sex, psychomotor retardation, aches and pains, sympathetic arousal, and leaden paralysis.

5.5. Discussion

Overall, based on the studies reviewed, there was evidence of a positive association between CRP with the somatic depression dimension and in particular those somatic symptoms related to appetite, sleep, and fatigue. However, the results across the reviewed studies were mixed. The findings for associations between the other inflammatory markers (IL-6 and TNF-a) and depression dimensions, subtypes or symptoms was much less consistent, particularly with TNF-a, although fewer studies were identified for these markers compared to CRP. The results did not support associations between inflammatory markers with the psychological depression domain, and the evidence was much weaker for associations between inflammatory markers

with individual symptoms from the psychological domain. There was also some support for an association between higher CRP with atypical depression. The findings for associations between the other inflammatory markers with atypical and melancholic depression were too inconsistent to draw firm conclusions but could be the subject of future research. There was also evidence of associations between CRP with appetite changes, sleep disturbance, and fatigue, and where the symptoms related to appetite were disaggregated with the components of metabolic syndrome, such as BMI, mediating some of these relationships. These points are discussed below.

Over two-thirds of the studies reviewed found a link between raised CRP with higher somatic symptom presentation (Case & Stewart, 2014; Duivis et al., 2013; Elovainio et al., 2009; Foley et al., 2021; Iob et al., 2020; Jokela et al., 2016; Michal et al., 2013; Milaneschi et al. 2021; Straka et al., 2020; White et al., 2017), although three of these were no longer significant after adjusting for covariates (Duivis et al., 2013; Michal et al., 2013; Milaneschi et al. 2021), and the rest had null findings even pre-adjustment (Bremmer et al., 2008; Dannehl et al., 2014; Euteneuer et al., 2017; Köhler-Forsberg et al., 2017; J. Krogh et al., 2014). Just under half of the studies examining links between IL-6 with somatic depression found a positive association (Duivis et al., 2013; Hazeltine et al., 2022; Milaneschi et al., 2021; Straka et al., 2020), but only one remained associated after full adjustment (Straka et al., 2020), and the results were similar for TNF-a, with only one study with a significant association between raised TNF-a with somatic depression post adjustment (Peters et al., 2021). There was no robust support for an association between any of the inflammatory markers with psychological depression dimension, based on the studies included in this review, but some support for an association with symptom constructs that mapped to anhedonia.

However, even for CRP the findings across studies were still mixed with some studies finding no significant positive associations with somatic depression (Bremmer et al., 2008; Köhler-Forsberg et al., 2017; J. Krogh et al., 2014; Michal et al., 2013). A key problem with comparing studies in this research area is that there are often high levels of variability in terms of what symptoms are included in the somatic symptom dimension. In this review, for example, most studies classed anhedonia as a psychological symptom, but some classed it as somatic (e.g. Foley et al., 2021; Schmidt et al., 2016). A few studies reviewed here included loss of libido as a somatic symptom (Elovainio et al., 2009; Foley É et al., 2021), but most did not include it. The most commonly included symptoms on the somatic scale were those related to appetite, sleep, and fatigue, with most studies measuring appetite and to a lesser extent sleep as compound symptoms, whereby the nature of the appetite change, or sleep disturbance is not defined. This of itself could be contributing to the inconsistent findings, as CRP is more likely to be associated with increased appetite (more on this below), and one study which did not find

any associations between CRP with the somatic subscale, only measured decreased appetite and sleep (Köhler-Forsberg et al., 2017).

Therefore, differences in results between studies may be down to the different symptom profiles that are being used to construct somatic depression, and this point has been noted in an earlier review (Majd et al., 2020). Going forward long term, standardising what symptoms constitute somatic depression would facilitate more meaningful study comparisons, and in the short term, replicating previous studies or including measures of depression at the symptom-item level would help progress our understanding of what may be driving associations with somatic depression.

This lack of standardisation also impacts the relevance of sickness behaviour theory as an explanation for the associations between inflammation and somatic depression. Most studies investigating the inflammation-somatic depression relationship measured appetite, and to a lesser extent sleep, as compound symptoms, whereby both increased and decreased changes were conflated. This aggregation of increased and decreased changes into one symptom undermines a more nuanced understanding of the associations between inflammation with sleep and appetite symptoms. It also leads to a loss of important information relevant to sickness behaviour theory as the appetite symptom associated with this theory, based on the work of pioneers in this area is decreased appetite, not increased appetite (Dantzer & Kelley, 2007). Therefore, symptoms related to appetite should be measured as disaggregated into increased and decreased to gain a fuller understanding of whether sickness behaviour applies (or at least in its traditional form) or whether the association may be being driven more by metabolic factors.

Overall, there was support for an association between CRP with atypical depression, with seven of the 10 studies reviewed finding higher levels of CRP associated with atypical depression (Badini et al., 2022; Glaus et al., 2014; Hickman et al., 2014; Lamers et al., 2013; Liu et al., 2022; Moilanen et al., 2024; Simmons et al., 2020), but two of these became non-significant after adjusting for metabolic syndrome components, such as BMI (Glaus et al., 2014; Liu et al., 2022). Brydges et al. (2022) found a link between atypical depression with an inflammatory index based on CRP and IL-6. Two studies discovered the reverse, higher CRP in melancholic depression compared to atypical (Karlovic et al., 2012; Rothermundt et al., 2001), but in one of these (Rothermundt et al., 2001) those in the melancholic depression group also had significantly higher depression severity compared with the somatic group, so the result could have been driven by a link between CRP with depression severity. For IL-6, the results were more inconsistent as three studies found IL-6 was higher in melancholic depression compared to controls (Dunjic-Kostic et al., 2013; Karlovic et al., 2012; Spanemberg et al., 2014), and two detected higher levels of IL-6 in atypical depression compared to both the melancholic group and controls (Lamers et al., 2013; Rudolf et al., 2014). For the studies that analysed

relationships between depression subtypes and TNF-a, most found no significant associations with either melancholic or atypical depression.

The most consistent associations between inflammatory markers and individual depression symptoms were found between CRP with symptoms related to appetite changes, sleep disturbances, and/ or fatigue/ energy related symptoms. Seven studies discovered associations between CRP with appetite changes (with appetite measured as a compound symptom (Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016; Kappelmann et al., 2021; Lee et al., 2023; Milaneschi et al., 2021; Moriarity et al., 2021), although in the Fried et al. (2020) study this association lost significance after adjusting for additional covariates, including BMI. The review also discovered evidence for associations between CRP with fatigue / loss of energy (Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016; Lee et al., 2023; Manfro et al., 2022; Moriarity et al., 2021), and sleep disturbances (Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016; Manfro et al., 2022; Moriarity et al., 2021; Sharpley et al., 2019). Symptoms related to appetite often co-occur with those related to sleep, with 74% of depressed patients reporting both (Caroleo et al., 2019) and the review found this to be the case with most studies reporting associations between CRP with appetite changes also finding associations with sleep disturbances (Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016), where measured (Sharpley et al., (2019) only assessed associations with fatigue).

When the symptoms related to appetite were disaggregated into increased and decreased, increased appetite was more likely to be associated with CRP (Chae et al., 2022; Milaneschi et al., 2021; Shell et al., 2022), however, in two of these studies the association was no longer significant after adjusting for BMI and other metabolic syndrome components (Chae et al., 2022; Milaneschi et al., 2021) and Shell et al. (2022) found insulin resistance and BMI mediating the relationship. For sleep, CRP was associated with both hypersomnia and insomnia. Milaneschi et al. (2021) found links between raised CRP with hypersomnia; Chae et al. (2022) detected raised CRP with insomnia; and for two studies higher CRP was linked to both insomnia and hypersomnia (Fried et al., 2020; Shell et al., 2022). In Chae et al. (2022), the association was no longer significant after adjusting for metabolic markers and in Shell et al. (2022), CRP was partly mediating the associations between hypersomnia and insulin resistance. There was also some evidence for links between higher CRP with symptoms related to anhedonia (Frank et al., 2021; Köhler-Forsberg et al., 2017; Manfro et al., 2022), and this association was just outside significance for Jokela et al. (2016).

There were far fewer studies investigating the relationships between IL-6 or TNF-a with individual symptoms compared to CRP, and no consistent results. In contrast with the findings for CRP with increased appetite, two studies found associations between raised IL-6 with decreased appetite (Milaneschi et al., 2021; Manfro et al., 2022), although Simmon et al. (2020)

found higher IL-6 in the depressed group with increased appetite. One study found an association between higher IL-6 with worthlessness (Frank et al., 2021) and Fried et al. (2020) found IL-6 positively associated with trouble falling asleep, sleep too much, aches and pains and negatively with irritability. Motivala et al. (2005) found elevated IL-6 levels corresponded with sleep disturbance amongst depressed group. For TNF-a, only two studies were retrieved, one discovered links between higher TNF-a with fatigue and another with trouble falling asleep, sleep too much, aches and pains and irritability (Fried et al., 2020).

Throughout this review, significant findings have been rendered non-significant after adjusting for various covariates, in particular those related to an unhealthy lifestyle. In Duivis et al. (2013) significant associations between somatic symptoms and CRP, IL-6, and TNF-a remained after adjustment for socio-demographic and health variables, but became non-significant after including variables measuring smoking, physical activity, and BMI. Similar results occurred in two other studies, in relation to both CRP and IL-6 for Milaneschi et al. (2021), and for CRP for Michal et al. (2013). A significant association between CRP with atypical depression became non-significant in Glaus et al. (2014) after adjustment for age, gender, and SES, but moved further from significance after including medication and cardiovascular risk factors (physical inactivity, smoking, BMI, and relevant medical conditions such as diabetes and hypertension). Adjusting for 'other' depression symptoms also had important implications for the results. Three studies showed significant associations between psychological depression with raised CRP pre adjusting for the influence of somatic symptoms, all of which became non-significant after this adjustment (Jokela et al., 2016; Case & Stewart, 2014; White et al., (2017).

Adjusting for covariates also affected associations between inflammatory markers with atypical depression and individual symptoms. Associations between CRP with increased appetite, decreased appetite, psychomotor retardation and fatigue were only significant in the univariable models in Chae et al. (2023) and became non-significant before the inclusion of BMI and other metabolic syndrome components, for example. Fried et al. (2020) found that the associations between CRP, IL-6 and TNF-a with appetite changes all became non-significant after covariate adjustment. These findings indicate the importance of adjusting fully for variables that may affect the inflammation-depression relationship, including using methodologies that take into account the effect of other symptoms, and prevent a link being found that is really the result of both factors being associated with a third variable, such as smoking or BMI, that is not included in the model.

The results from this review all highlight the importance of disaggregating symptoms related to appetite and sleep, if the true nature of any associations between these symptoms with inflammatory markers is to be discerned. The review found that CRP was more likely to be associated with increased appetite, and two studies found IL-6 linked with decreased appetite,

although the evidence for IL-6 with decreased appetite was weak and would need replication. BMI has been found to have a pivotal role in the relationship between increased appetite and raised CRP. In Milaneschi et al. (2021), adjusting for BMI led to the association becoming non-significant and Shell et al. (2022) found that CRP and BMI were mediating relationships between insulin resistance and increased appetite. Results such as these have led researchers to a model of depression based on immuno-metabolic dysregulation, termed immune-metabolic depression (IMD), which aligns with atypical depression symptoms, particularly increased appetite, and is characterized by elevated CRP levels and components of metabolic dysregulations, such as high BMI. Those depressed groups with the IMD subtype may benefit more strongly than other depressed groups from treatments that lower inflammation and target metabolic dysfunction (Milaneschi et al., 2020; Simmons et al., 2020).

5.6. Conclusion

Overall, the review showed that associations between inflammatory markers and depression were more likely with certain depression dimensions or depression subtypes, namely those characterised by physical symptoms, somatic and atypical depression, and for those symptoms characteristic of these depression domains and subtypes: those related to appetite, sleep, and fatigue. When the symptom related to appetite was disaggregated, there was evidence that increased appetite was associated with CRP, but not decreased, indicating the importance of disaggregating symptoms related to appetite (and sleep) to prevent associations with inflammation being obscured and more nuanced relationships discovered. The review also reinforced the importance of adjusting for all other depression symptoms and relevant covariates, particularly those related to an unhealthy lifestyle that have been found to be associated with both depression and inflammation, such as BMI, smoking, alcohol, physical activity, and certain chronic diseases, to prevent misleading findings. Overall, the results of the review support the perspective that when investigating associations between inflammation and depression, depression should be measured in ways that can capture the heterogeneity of symptom profiles, potentially alongside other measures that can take into account depression severity, if progress is to be made in identifying biomarkers for depression.

Chapter Prelude Chapter 6

This chapter investigated links between inflammation (as indexed by CRP, IL-6 and TNF-a) with depression, using network analysis. Depression was measured in two ways: in terms of the two main depression dimensions (psychological and somatic), and as individual symptoms. It was a procedural replication of three previous network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021) and but extended them, primarily in the ways it measured the symptoms related to appetite and sleep. As well as modelling appetite and sleep symptoms as compound symptoms, which combines increased and decreased disturbances into one measure of disturbance, as per these other network studies, it additionally modelled them as disaggregated symptoms, where the nature of the disturbance, increased and decreased, is accounted for.

Chapter 6. Associations between Inflammatory Biomarkers and Depression amongst Pacific NZ Young Adults

6.1. Introduction

It is estimated that around 5% of adults (defined as 20 years and over) globally suffer from depression, which is the leading cause of disability worldwide (WHO, 2023). Depression is closely associated with poor physical health, the inability to work, study or form quality relationships, and suicide (the fourth leading cause of death in 15–29-year-olds worldwide (WHO, 2023). Depression is a particular problem in NZ. In an international survey, NZ had the fourth highest 12-month prevalence of depression (6.6%) out of all the countries surveyed (high income and low-middle income), and the second highest out of the high-income countries (Kessler & Bromet, 2013).

Within NZ, a recent report found that young people (aged 15-24) were particularly affected by psychological (mental) distress, with over 20% reporting that they experienced high or very high levels of psychological distress[17] (Ministry of Health, 2023). This was a large increase compared to 2011/12, when only 5.1% reported experiencing such high levels (Ministry of Health, 2022). The COVID-19 pandemic contributed to this rise globally (WHO, 2022), including in NZ (Siegert et al., 2023), but the trend had been increasing over time pre-pandemic, particularly amongst young adults. According to a health report, around 15% of 15-24 year olds in NZ reported high levels of psychological distress in 2018/19 (Ministry of Health, 2019). In NZ, this group (15-24 year olds) also have the highest suicide rate, at 20.4 (per 100,000 people), which is almost double the rate of the age group with the lowest rate (65 years plus) (The Treasury, 2022). A report into Pacific mental health and wellbeing found that severity of psychological distress was significantly higher in Pacific people compared to Others (a composite ethnic group comprised of non-Pacific and non-Māori people[18]), and amongst Pacific people the prevalence of medium to high levels of psychological distress was highest for young Pacific people aged 15-24 years, at 38% (Health Promotion Agency, 2018).

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1 Psychological, or mental, distress (aged 15+ years) refers to a person's experience of symptoms such as anxiety, psychological fatigue, or depression in the past four weeks. It is measured using The Kessler Psychological Distress Scale (K10). A K10 score of 12 or more is strongly associated with having a mental (depressive or anxiety) disorder (Kessler et al 2003).

[18] Māori people in NZ are also more likely to suffer from psychological distress than Others and NZ Europeans, and whilst this is of concern, Māori people are not the focus of this research.

6.1.1. The Link between Depression and Systemic Inflammation

Depression remains an elusive disease. It is often mis-diagnosed and undertreated (Kaye et al., 2000). Diagnosis and treatment are complicated by illness heterogeneity and co-occurrence with many other non-communicable diseases (Fried et al., 2014). Biological mechanisms underpinning depression have been investigated in an attempt to better understand aetiology, classification and treatment. Chronically raised, low-grade systemic inflammation has been implicated in the pathophysiology of depression and may represent a biomarker with diagnostic and prognostic utility (Berk et al., 2013; Bullmore, 2018; Raison et al., 2006). Whilst several large meta-analyses support higher levels of inflammatory molecules (e.g., Interleukin-6 (IL-6), Tumour Necrosis Factor alpha (TNF-a), Interleukin-1 beta (IL-1b), and C-reactive protein (CRP) in depression (Bizik, 2010; Dowlati et al., 2010; Goldsmith et al., 2016; Haapakoski et al., 2015; Hiles et al., 2012; Howren et al., 2009; Kohler et al., 2017), effects sizes vary, and some studies have failed to identify any relationships between inflammatory biomarkers and depression (e.g. Bizik et al., 2014; Steptoe et al., 2003). Stronger associations have been found between depression and inflammatory biomarkers in clinical populations, compared to community samples (Hiles et al., 2012; Howren et al., 2009). However, in the general population inflammation has been seen in relation to self-reported personality traits implicated in risk for depression (Heym et al., 2019; Sumich et al., 2022). Some multivariable models show the relationship to be explained by Body Mass Index (BMI), and other indicators of unhealthy lifestyles (e.g., alcohol consumption, smoking, physical activity (de Menezes et al., 2017; Duivis et al., 2013; Gialluisi et al., 2020)). The way depression is analysed might also affect findings. For example, Dannehl et al. (2014) showed higher TNF-a in depression relative to healthy controls, but there were no significant cross-sectional relationships between TNF-a with depression sum scores or any depression subscales for the sample as a whole. In a meta-analysis, Horn et al. (2018) showed that effect sizes for an association between CRP and depression were substantially reduced after selecting a sub-sample of studies based on quality of covariate adjustment. Furthermore, the effect size became non-significant when only those studies with the highest quality scores, based on methodological rigour, were included (Horn et al., 2018). Negative correlations between biomarkers and depression have also been found (Schmidt et al., 2016).

Various reasons have been put forward to explain these inconsistent findings. These have primarily focused on the variations between studies in terms of the nature of sampling (clinical versus community); characteristics of the sample (in terms of age, gender, and ethnicity, for example); inflammatory markers studied; covariates adjusted for (as outlined above); and the heterogeneous nature of depression *per se* (Fried et al., 2020; Hiles et al., 2012; Horn et al., 2018; Majd et al., 2020). Overall, meta-analyses suggest great variation across studies investigating relationships between inflammation and depression (Dowlati et al., 2010; Hiles et

al., 2012; Kohler et al., 2017), rendering direct comparisons between studies difficult. There are also high levels of heterogeneity amongst participants within studies, increasing the risks that unadjusted confounding effects could render inaccurate or misleading findings. Another possible, relatively unexplored factor potentially contributing to inconsistent findings is the differences in the statistical methodologies used to assess whether a significant association exists or not.

There is a growing acceptance that certain subgroups of depressed people exhibit elevated inflammation (Berk et al., 2013; Osimo et al., 2019; Raison & Miller, 2011), but what characterises these subgroups remains an area of ongoing research. One theory gaining traction is that the association between depression and inflammation is symptom specific and can be obfuscated when depression is measured as a sum score of symptoms or Major Depressive Disorder (MDD) diagnosis (Fried et al., 2014; Fried et al., 2020). Other risk factors for depression have been found to be differentially associated with symptoms (Fried et al., 2014; Gossage et al., 2022). A large body of research has found that associations between depression and inflammation are more likely for those symptoms which have physical manifestations, such as symptoms related to appetite changes, sleep disturbances, and/ or fatigue (Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016; Lee et al., 2023; Moriarity et al., 2021) and the depression dimension characterized by these physical symptoms, somatic depression[19] (Case & Stewart, 2014; Iob et al., 2020; Majd et al., 2020). Associations have also been found between inflammatory biomarkers and symptoms of anhedonia (Felger, 2023; Felger, 2017; Freed et al., 2018; Köhler-Forsberg et al., 2017; Moriarity et al., 2020).

6.1.2. The Importance of Disaggregating Symptoms Related to Appetite

One theory put forward for associations between inflammatory markers and physical symptoms of depression is Sickness Behaviour Theory (e.g. Frank et al., 2021; Jokela et al., 2016; Majd et al., 2020). According to this theory, symptoms such as loss of appetite, sleepiness, and fatigue, which overlap with symptoms of sickness or infection, are the result of upregulated inflammation (Dantzer, 2006; Dantzer & Kelley, 2007). Often the symptom constructs

[19] The DSM-IV lists three criteria for somatic symptoms for major depressive disorder: sleep disturbance, appetite disturbance, and fatigue or loss of energy American Psychiatric Association, D., & Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5). American psychiatric association Washington, DC. The ICD-10 lists sleep, appetite, loss of libido, and amenorrhea as somatic symptoms of diagnostic significance WHO. (2023). *Depressive disorder (depression)*. Retrieved 28/06/2023 from https://www.who.int/news-room/fact-sheets/detail/depression. The somatic dimension of depression assessed using subscales, based on inventories of depression symptoms, varies depending on the inventory used, but usually includes symptoms related to sleep, appetite, and fatigue, and may include other symptoms with physical rather than psychological presentations.

measuring appetite or sleep disturbances are conflated, with both increased and decreased disturbances aggregated into one symptom (e.g. Case & Stewart, 2014; Duivis et al., 2013; Frank et al., 2021; Fried et al., 2020; Jokela et al., 2016; Lee et al., 2023; Moriarity et al., 2021). This might obscure associations with inflammatory markers, as there is evidence that the biological profiles of those depressed subjects with increased as opposed to decreased appetite differ (Lamers et al., 2018; Milaneschi et al., 2021; Simmons et al., 2020).

In studies that have measured appetite as a disaggregated symptom, increased rather than decreased appetite has been found to be associated with higher levels of inflammation (Lamers et al., 2018; Simmons et al., 2020), although Milaneschi et al. (2021) found divergent associations for appetite changes, with increased appetite associated with higher CRP and decreased appetite with higher IL-6; and the association between CRP and increased appetite became non-significant after adjusting for BMI (Milaneschi et al., 2021).

Similarly, atypical depression, a subtype which is characterized by increased appetite, has been associated with raised levels of inflammatory markers, whilst nonatypical (melancholic or typical depression) has not (Glaus et al., 2014; Hickman et al., 2014; Lamers et al., 2013; Milaneschi et al., 2020). For example, Lamers et al. (2013) found both CRP and TNF-a (but not IL-6) positively associated with atypical depression, but only TNF-a after adjusting for BMI. In comparison, other authors (Milaneschi et al., 2021; Glaus et al., 2014) report an association between CRP (but not TNF-a) and atypical depression, again only prior to adjusting for BMI. Simmons et al. (2020) observed elevation in both IL-6 and CRP in those with depression and increased appetite. Hickman et al. (2014) only measured CRP, and the association with atypical depression remained significant and only slightly attenuated after including BMI.

Higher BMI and other markers of metabolic dysregulation (e.g. higher waist circumference, and higher insulin and leptin levels) have also been found to be associated with atypical depression and the depression symptom increased appetite, as well with CRP (Lamers et al., 2018; Milaneschi et al., 2020; Simmons et al., 2020), and adjusting for BMI has often rendered associations between CRP and atypical depression or increased appetite non-significant, as outlined above. These findings have led the authors to suggest that it is components of metabolic dysregulation, and their dual associations with both depression (or depression subtypes) and inflammation that is driving the link between depression and inflammation (Lamers et al., 2018; Milaneschi et al., 2017; Simmons et al., 2020). This has prompted recommendations for a depression model based on immuno-metabolic dysregulation (immuno-metabolic depression (IMD)), which maps to atypical depression symptoms, in particular increased appetite, and is accompanied by higher levels of CRP and BMI (Milaneschi et al., 2020; Simmons et al., 2020).

6.1.3. The Present Study

The present study used network analysis to investigate direct and indirect associations between the inflammatory markers CRP, IL-6, and TNF-a with individual depression symptoms as well as with psychological and somatic depression dimensions, in a sample of Pacific NZ young adults. Based on previous research as outlined above, we hypothesised that associations between inflammatory markers and depression would be symptom specific and positive associations would be more likely between CRP with symptoms of depression from the somatic scale, and most likely for those symptoms that also characterize the atypical depression subtype (i.e., increased appetite, hypersomnia, fatigue) after adjusting for all other depression symptoms and potential confounders. It was also hypothesized that the associations would be attenuated after adjusting for potential confounders, including those markers of an unhealthy lifestyle, such as smoking, alcohol consumption, BMI, and physical activity. The analysis of indirect associations was exploratory as previous studies have not specifically investigated these.

The current study was a procedural replication of three recent network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021)[20], but extended the procedures used in these studies in a number of ways. Primarily, it measured symptoms related to sleep and appetite both as composite symptoms, whereby the direction of the disturbance (increased or decreased) was conflated into one symptom, and as disaggregated symptoms (which separated out the nature of the disturbance into increased or decreased). All these previous network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021) measured appetite disturbances only as a composite symptom and two also measured sleep disturbances as composite (Lee et al., 2023; Moriarity et al., 2021). Disaggregation of these items is important as the direction of appetite change is a major discriminating factor for the identification of subtypes of depression (Simmons et al., 2020; ten Have et al., 2016), and the nature of the association with inflammation may differ depending on the direction of appetite change, as outlined above (see 6.1.2 The importance of disaggregating symptoms related to appetite).

The current study also investigated associations between inflammation and two depression dimensions: psychological and somatic. Fried et al. (2020) measured depression in terms of an overall depression sum score and by individual symptom items; Moriarity et al. (2021) and Lee et al. (2023) as individual symptom items only. The present study investigated indirect as well as direct associations between inflammatory biomarkers and depression, tested for moderators, and investigated possible mediators. Finally, as well as using the same statistical methodologies

[20] The study Moriarity et al. (2021) was a procedural replication of that by Fried et al. (2020), and Lee et al. (2023) of the study by Moriarity et al. (2021).

to estimate the networks as those used across these three network studies, it included an additional statistical method to investigate how statistical methodologies influence findings (see 6.2.3 Data analysis section for more details).

In addition, our study contributed valuable information to the repository of studies investigating inflammation-depression links, as it was the first to investigate associations between inflammation and depression in Pacific people in NZ. Relevant research with a wide range of ethnic/ racial groups is important, as the inflammation-depression relationship may differ by race/ ethnicity (Case & Stewart, 2014; Morris et al., 2011).

6.2. Methods

6.2.1. Source of Data and Participants

The present study was cross-sectional in design and used primary data collected during the year-20 wave of the Pacific Islands Families (PIF) Study. The PIF Study is an ongoing longitudinal study of a birth cohort of 1398 Pacific children born at a South Auckland hospital in NZ in the year 2000. To date, data have been collected at regular intervals from 6 weeks onwards. Eligibility criteria for the PIF Study included having at least one parent who identified as being of a Pacific ethnicity, with permanent residency in NZ. Further information on the PIF Study and characteristics of the cohort are available elsewhere (Paterson et al., 2008). The PIF study has been guided by the Pacific People's Advisory Group and approved by Auckland University of Technology Ethics Committee (AUTEC) (references 17/26 and 19/364 apply).

The current analysis used data collected between February 2020 and April 2021, the year when the youth cohort turned 20, with interruptions due to COVID-19 alert level restrictions (for more information on COVID-19 alert levels and timelines (Department of the Prime Minister and Cabinet, 2023). A total of 377 participants completed questionnaires relating to psychological and covariate data and out of these 257 provided blood samples. To avoid the potential confounding effects related to severe medical conditions and acute inflammation, participants with chronic diseases (e.g. diabetes, heart disease, or cancer), and/ or CRP levels over 10mg/L (n=14) were excluded from the current study, plus four participants whose biomarker data was unable to be measured. The final analytic sample for this study therefore consisted of 239 participants. Missing data for the analysis variables was minimal (3% or less), and data were imputed with a multiple imputation method using the R package missForest (Stekhoven & Bühlmann, 2012) (Chapter 2 Methods and Measures, section 2.2 Missing Data and Participant Exclusion for more information on missing data analysis and the imputation strategy).

6.2.2. Measures

6.2.2.1. Inflammatory Biomarkers

The data for the biomarkers being investigated (CRP, IL-6, and TNF-a), were collected through serum blood samples. Special tubes without anticoagulant or Serum Separator Tubes (SST, BD Vacutainer®) were used to collect blood samples (one 13 x 75 mm x 8.5 mL tube per fasting participant) and inverted 5 to 10 times to activate clotting before leaving the tubes undisturbed in an upright position at room temperature for 30 minutes. Tubes showing signs of haemolysis were discarded as haemoglobin may interfere with some tests. Tubes were kept at low temperature (+4°C) and immediately transported to the AUT Roche Diagnostics Laboratory where they were centrifuged to get the serum samples. As specimens were processed in batches, serum samples were stored at -20°C to ensure the stability of the biomarkers over time.

6.2.2.2. Depression Symptoms

Psychological depression symptoms were measured using the Beck Depression Inventory (BDI) - Fast Screen (BDI-FS) (Beck et al., 2000), a short version of the 21 item BDI-II (Beck, 1996), which omits somatic symptoms and has shown good reliability in general populations (Kliem et al., 2014). Somatic depression symptoms were measured using BDI-II items 15–21 as has been used elsewhere (Thombs et al., 2010). For all depression symptoms, except those relating to sleep and appetite, possible responses ranged from 0-3 on a Likert scale, with 0 representing an absence of that symptom, and 1 to 3 its presence, with higher scores denoting higher symptom severity. For the symptom related to feeling sad, for example, possible options were: 0 = I do not feel sad, 1 = I feel sad, 2 = I am sad all the time, and 3 = I am so sad I can't stand it. Participants were asked to mark the response that best described how they felt about an item, relevant to the previous fortnight. For the sleep and appetite symptoms, there were seven possible options (coded 0, 1a, 1b, 2a, 2b, 3a, and 3b), to enable both increases and decreases in sleep and appetite to be captured. No disturbances of any kind for sleep and appetite were represented by 0, and then there were three options of increasing severity each for both increased and decreased sleep and appetite. For example, for the symptom relating to appetite changes, the options 1a, 2a, and 3a related to rising severity of decreased appetite, with 1a = appetite somewhat less than usual, 2a = appetite much less than usual, and 3a = no appetite at all; and options 1b, 2b, and 3b related to increased appetite, with 1b = somewhat greater than usual to 3b = craving food all the time. The symptom relating to sleep changes followed a

similar pattern, except that 1a, 2a, and 3a represented increasing severity of hypersomnia, and 1b, 2b, and 3b[21] of insomnia.

For the analyses of individual depression symptom items, all symptoms, except those related to sleep and appetite, were dichotomized into 1/0= presence/absence of the symptom, due to small cell counts in the levels of certain symptoms and the skewed distributions of the symptoms[22]. All non-zero responses were regarded as presence of a symptom. As the two BDI-II items relating to sleep and appetite included options for both increased and decreased sleep or appetite, the sleep and appetite symptoms were composed in three different ways:

- As composite symptoms, dichotomized into presence / absence of the symptom irrespective of the nature of the disturbance (1/0 = presence / absence), termed *Sleep disturbance*[23] and *Appetite disturbance.* For example, for *Sleep disturbance*, presence was defined by any responses that represented sleep decreases or increases (1a, 1b, 2a, 2b, 3a, or 3b) and were coded 1, and absence was defined as the response representing no disturbances (0) and coded 0. The same pattern of coding was followed for *Appetite disturbance*.

- As disaggregated symptoms, also dichotomized, but with separate symptoms created for increased and decreased appetite and sleep disturbances, termed *Increased sleep, Decreased sleep, Increased appetite,* and *Decreased appetite*. For example, *Decreased appetite* was defined by any responses that represented appetite decreases (1a, 2a, or 3a) and were coded 1, and absence by responses representing no disturbances to appetite plus any responses that related to increased appetite (responses 0, 1b, 2b, or 3b), and were coded to 0. The same pattern of coding was followed for the other disaggregated symptoms.

- As 3-level categorical variables with each level corresponding to the nature of the disturbance (1 = none (no disturbance of any kind), 2 = less (that is disturbances leading to decreased sleep, or decreased appetite in case of that symptom), and 3 = more (that is

[21] In the question relating to sleep, there was a small error in the survey. The option should have read 'I wake up 1-2 hours early and can't get back to sleep' but instead was 'I wake up 0-1 hours early and can't get back to sleep'. However, there was evidence that participants had accepted this option as most severe, based on ordinality of data and as all levels relating to decreased sleep were combined into one level for the symptom analyses, it was judged that this would have minimal impact on findings.

[22] The other network studies (Fried et al., 2020; Lee at al., 2023; Moriarity et al., 2021) that this study was procedurally replicating measured depression symptoms as continuous.

[23] When variables from this study are referred to in the text, they are denoted by capital first letter and italics, for example *Sleep disturbance*, to differentiate them from general use of such terms.

disturbances leading to increased sleep, or increased appetite for that symptom), termed *Sleep disturbance 3-level*, and *Appetite disturbance 3-level.* For example, for *Appetite disturbance 3-level*, those responses representing no disturbance (0), were coded to level 1, any responses representing decreases in appetite (1a, 2a, and 3a) were coded to level 2, and any increases in appetite (1b, 2b, and 3b) were coded to 3. The same pattern of coding was followed for *Sleep disturbance*.

6.2.2.3. Depression Subscales

To assess the severity of psychological and somatic dimensions of depression, two subscales were created. *Psychological depression* was assessed by summing the 7 items on the BDI-FS (Beck et al., 2000). *Somatic depression* was assessed by summing the items 15-21 of the BDI-II (Beck, 1996). Higher scores denoted higher severity of that depression dimension. When summing symptom scores to create the depression subscales, the items related to sleep and appetite were recoded into 4 levels of increasing severity (0,1,2, and 3), irrespective of the nature of the disturbance, and given a score of 0 to 3 as per the other symptoms. Cronbach's alpha was used to check the internal consistency of summing items to make the two scales (Cronbach, 1951), using R package Psych (Revelle & Revelle, 2015). Results showed good internal consistency for both the psychological and somatic depression subscales, with alphas of .84 and .83, respectively. See Appendix C, Table C-1 for more information on depression symptom prevalence and depression subscale scores.

6.2.2.4. Covariates

Covariates were chosen to align with the three previous studies (Duivis et al., 2013; Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021), apart from age which was excluded in the present study as all participants were very close in age (Mean=19.85 (SD=0.35)). Covariates were *Gender* (0=male, 1=female)[24], *Smoking* (1=never, 2=past, 3=current), *Exercise* (0=no, 1=yes), *BMI*, and *Alcohol* consumption (assessed with the Alcohol Use Disorders Test of Consumption (AUDIT-C)) (Bush et al., 1998).

Gender and *Exercise* were modelled as binary variables, and the inflammatory markers (*CRP, IL-6*, and *TNF-a*), *BMI*, *Alcohol*, and *Smoking* as numeric variables. All depression and covariate data were self-report measures apart from *BMI* (calculated as weight in kilograms divided by height in metres squared (kg/m^2), which was composed of both self-reported data

[24] Participants were given the options of male, female and prefer not to say. Three participants from the full sample marked 'prefer not to say' but this response was coded as missing data as the numbers were too small to analyse separately.

(for weight and height) collected during the year-20 data collection wave and, supplemented with weight and height measurements collected accurately by study assessors during the year-17 data collection wave. When it was necessary to use year-17 BMI data, a growth factor was added to the year-17 BMI data, based on BMI growth charts from the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2022). See Chapter 2 Methods and Measures, section 2.4 Measures Chapter 6 for more details of how *BMI* and other covariates were composed.

The effect of COVID-19 alert level restrictions was not controlled for due to the difficulty in accurately and reliably assessing the impact of COVID-19 on the data. A small number of participants completed questionnaires and had bloods taken pre any COVID-19 alert levels (n=20), but after the reporting of COVID-19 cases in NZ, in the run-up to the first lockdown. The rest of the data was collected between lockdowns, when COVID-19 alert levels permitted this. However, as all data was collected during the period of high COVID-19 media coverage and given that the sample was homogeneous, with regard to age, Pacific ethnicity[25], and location (all lived in Auckland), it was considered reasonable to assume that all participants were similarly affected by the COVID-19 events.

6.2.3. Data Analysis

Statistical analysis was completed using statistical software R (R Core Team, 2020) augmented by various R packages. As all the numeric variables had skewed distributions, they were normalized using the non-paranormal transformation (Liu et al., 2009)

6.2.3.1. Network Estimation

Several network models were fitted to the data using the mgm package in R, which enables network modelling of different data types (continuous, binary, and categorical) (Haslbeck & Waldorp, 2020). Networks are increasingly being used to capture complex associations between variables relevant to mental disorders, where nodes usually represent variables, including but not limited to the symptoms of a mental disorder, and edges represent the conditional relationships between them (Borsboom & Cramer, 2013; Borsboom et al., 2021; Epskamp et al., 2018; Haslbeck & Waldorp, 2020). The term “conditional” in this context means that an edge between two variables cannot be explained away by any of the other variables included in the

[25] In this study Pacific New Zealanders are treated as one ethnic group, but each Pacific island community does have its own cultural characteristics. However, Pacific people share several cultural values, including spirituality, collectivism, importance of family, and behaving respectfully, particularly towards elders and people in positions of authority. See Ministry of Pacific Peoples (2022). Yavu. Foundations of Pacific Engagement.

network[26]. The mgm-package uses neighbourhood nodewise regression to estimate parameters, which are then combined into an edge weight (w) representing an absolute value that quantifies the strength of an association (see Chapter 2 Methods and Measures, section 2.5 Data Analysis, subheading 2.5.1 Network Estimation, subheading 2.5.1.2 Estimation of Edge Weights for more details of how the parameters are combined into edge weights).

To control for false positives, least absolute shrinkage and selection operator (LASSO) (Tibshirani, 1996) was implemented. LASSO is a regularization method where small edge weights are shrunk to zero via a penalty parameter lambda and non-zero estimates are highlighted by the presence of an edge. Lambda was selected in two ways: 1) using Extended Bayesian Information Criterion (EBIC) (Chen & Chen, 2008; Foygel & Drton, 2010), as per Fried et al. (2020) and Moriarity et al. (2021); and using cross validation (CV) (Hastie et al., 2009) which has a lower specificity and a higher sensitivity than with EBIC (Wysocki & Rhemtulla, 2021). Regularization with EBIC also uses a tuning parameter, gamma, with higher gamma values favouring parsimonious models. The gamma parameter in the model was set at 0 for the main network models because associations between variables from different domains (e.g. between depression symptoms (psychological domain) and inflammatory markers (biological domain)) are likely to be much weaker than associations between variables from the same domain (e.g. between symptom-symptom associations) and so are more likely to be shrunk to zero by the LASSO (Epskamp & Fried, 2018). This was also in line with methods used by Fried et al. (2020) and Moriarity et al. (2021). To enable comparisons with previous network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021), and as recommended elsewhere (Williams et al., 2019), networks were also fitted without regularization, but using a threshold (Loh & Wainwright, 2012), which is built into the mgm package (Haslbeck & Waldorp, 2020), to reduce the risk of false positives. Refer to Table 12 for the list and description of network models fitted to the data.

6.2.3.2. Nodewise Centrality and Predictability

Nodewise predictability was used to measure the extent to which a node could be explained by its neighbours. The strength and/ or the number of the edges connected to a node, the higher the predictability and the higher the likelihood that it could be affected by actions on neighbouring nodes (Haslbeck & Waldorp, 2018). Nodewise Predictability was quantified using proportion of variance explained by other network nodes for numeric nodes (similar to R-squared) and

[26] For example, if we have a chain graph A-B-C, then A and C are marginally dependent through B. However, when conditioning on all other variables (here only B), then A and C are conditionally (on B) independent. For more information on conditional independence see Dawid, A. P. (1979). Conditional independence in statistical theory. *Journal of the Royal Statistical Society: Series B (Methodological), 41*(1), 1-15.

normalized accuracy for the categorical nodes. The normalized accuracy is the amount of accuracy achieved by the model over and above the intercept only model. Two measures of centrality were also used to determine which nodes had the highest and/ or strongest connections in the networks: Strength and Degree (Barrat et al., 2004; Freeman, 2002; Opsahl, 2010). Strength is calculated by summing the absolute value of edge weights connected to a node and Degree by the number of edges connected to a node. It is important to separately measure both Strength and Degree centralities to gain an estimate of a node's overall importance, as a strong association between two nodes can lead to high Strength centrality, even if the nodes have low connectivity in the network (Hevey, 2018).

6.2.3.3. Network Reliability

Pairwise edge reliability was assessed by calculating edge probability inclusion rates (PIRs) derived from 500 non-parametric bootstrap samples, as used elsewhere (Fried et al., 2020; Moriarity et al., 2021). The PIR represents the percentage of bootstrap samples where the edge was non-zero (Epskamp et al., 2018). A high PIR of a given edge across bootstrap samples provides evidence for the presence of the edge in the population. In the unregularized networks, only edges with associated PIRs > 50% were reported, in line with other research (Kappelmann et al., 2021)[27], but for the regularized networks all edges were reported as regularizaton is itself a form of variable selection (Hastie et al., 2009). However, higher PIRs indicated higher reliability in both regularized and unregularized networks. The stability of the centrality metrics, Strength and Degree, were calculated using the correlation stability coefficient (CS-coefficient). Simulation studies have shown that the CS-coefficient needs to be >=0.25 for centrality metrics to be interpretable, and preferably >= 0.5 (Epskamp et al., 2018). See Chapter 2, section 2.6 Data Analysis for more information on how the CS-coefficient is calculated.

6.2.3.4. Network Visualization

Graphical representations of the network models were performed via the integration of the mgm package with qgraph package (Epskamp et al., 2012). The Fruchterman-Reingold algorithm was used in this procedure to place nodes with stronger connections closer together. In the network graphs, wider and more colour-saturated edges depicted stronger associations and the colour the direction of the association between two nodes: blue represented a positive association, red a negative association, and grey meant the direction could not be obtained from the network graph (as one of the variables was a categorical variable with more than 2 levels), but could be identified from post hoc investigations using methods available in the mgm package (Haslbeck

[27] In Kappelmann, Czamara, et al. (2021), three criteria were specified, including recovering edges in over 50% of bootstrapped resamples for the unregularized networks.

& Waldorp, 2020). The predictability of each node was shown by the shaded pie segment. This was light blue for numeric variables and represented R-squared; and for the categorical variables the yellow part of the segment represented the predictability of the intercept model, the red part the additional predictability by neighbouring nodes, and the sum of both segments the predictability of the whole model.

Table 12 Description of the network models used in the analysis

Network	Depression measure	Appetite and sleep symptoms	Covariates
1A (EBIC)	Subscales	n/a[a]	No
1A (CV)	Subscales	n/a	No
1A (Unregularized)	Subscales	n/a	No
1B (EBIC)	Subscales	n/a	Yes
1B (CV)	Subscales	n/a	Yes
1B (Unregularized)	Subscales	n/a	Yes
2CC (EBIC)	Individual symptoms	Appetite and Sleep disturbances (presence / absence)	No
2CC (CV)	Individual symptoms	As per above	No
2CC (Unregularized)	Individual symptoms	As per above	No
2CM (EBIC)	Individual symptoms	Increased appetite and Increased sleep	No
2CM (CV)	Individual symptoms	As per above	No
2CM (Unregularized)	Individual symptoms	As per above	No
2CL (EBIC)	Individual symptoms	Decreased appetite and Decreased sleep	No
2CL (CV)	Individual symptoms	As per above	No
2CL (Unregularized)	Individual symptoms	As per above	No
2CLM (EBIC)	Individual symptoms	Appetite and Sleep disturbances 3-level	No
2CLM (CV)	Individual symptoms	As per above	No
2CLM (Unregularized)	Individual symptoms	As per above	No
2DC (EBIC)	Individual Symptoms	Appetite and Sleep disturbances (presence / absence)	Yes
2DC (CV)	Individual symptoms	As per above	Yes
2DC (Unregularized)	Individual symptoms	As per above	Yes
2DM (EBIC)	Individual symptoms	Increased appetite and Increased sleep	Yes
2DM (CV)	Individual symptoms	As per above	Yes
2DM (Unregularized)	Individual symptoms	As per above	Yes
2DL (EBIC)	Individual symptoms	Decreased appetite and Decreased sleep	Yes
2DL (CV)	Individual symptoms	As per above	Yes
2DL (Unregularized)	Individual symptoms	As per above	Yes

2DLM (EBIC)	Individual symptoms	Appetite and Sleep disturbances 3-level	Yes
2DLM (CV)	Individual symptoms	As per above	Yes
2DLM (Unregularized)	Individual symptoms	As per above	Yes

[a]This measure was not applicable in these networks as they used sum scores of the symptom subscales to construct variables representing somatic and psychological depression

Notes on networks

All networks beginning with 1 measured depression in terms of two subscales: psychological and somatic.

All networks beginning with 2 measured depression in terms of individual symptoms.

All networks with the letter A or C, following network number 1 or 2, excluded covariates.

All networks with letter B or D, following network number 1 or 2, included covariates.

All networks with final suffix C measured sleep and appetite items as composite (presence/ absence), labelled *Sleep disturbance* and *Appetite disturbance*.

All networks with suffix M measured sleep and appetite items as disaggregated into more/ not more, labelled *Increased sleep* and *Increased appetite*.

All networks with suffix L measured sleep and appetite items as disaggregated into less/ not less, labelled *Decreased sleep* and *Decreased appetite*.

All networks with suffix LM measured sleep and appetite items as disaggregated into a 3-level symptom, where the levels represented none, less, or more, respectively, and labelled *Appetite disturbance 3-level* (None/ less/ more) and *Sleep disturbance 3-level* (None/ less/ more).

6.3. Results

The characteristics of the sample in terms of socio-demographic, health, and lifestyle variables are shown in Table 13. In terms of symptom prevalence, *Sleep disturbance* had the highest, with 62% reporting a disturbance of increased or decreased sleep, followed by *Appetite disturbance* with 54%. When these symptoms were disaggregated into separate measures for increased and decreased sleep and appetite, they no longer had the highest prevalence, and the symptom most frequently reported was *Loss of energy* with 49%. The symptom with the lowest prevalence was *Suicidal thoughts* (14%). See Appendix C, Table C-1 for summary statistics of the inflammatory biomarkers and depression measures.

Table 13 Characteristics of sample

Characteristic	n = 239[a]
Age	
Mean (SD)	19.85 (0.35)
Gender[b]	
Male	96 (40.2%)
Female	143 (59.8%)
Ethnicity	
Samoan	109 (45.6%)
Tongan	55 (23.0%)
Cook Islands Māori	37 (15.5%)
Other Pacific Islands[c]	15 (6.3%)
Other[d]	23 (9.6%)
Smoking	
Never	91 (38.1%)
Past	68 (28.4%)
Current	80 (33.5%)
Exercise	
Yes	72 (30.1%)
No	167 (69.9%)
BMI	
Mean (SD)	33.54 (7.62)
Median (IQR)	33.24 (27.65, 38.77)
Alcohol	
Mean (SD)	3.92 (2.95)
Median (IQR)	4.00 (1.00, 6.00)

[a] n (%)

[b] Participants were also given the option of 'Prefer not to say' and in the full sample (N=377), 3 chose this, but they were missing biomarker data and so were not included in the final analytic sample.

[c] This group was made up of those who identified as Tokelauan, Niuean, or Fijian.

[d] This group was made up of those who identified as Pākehā (European New Zealanders), Māori or multiple groups equally.

6.3.1. Direct Associations between Inflammatory Biomarkers and Depression Subscales

In the networks where depression was measured in terms of the subscales *Psychological depression* and *Somatic depression* (networks 1A and 1B), there were no edges between the inflammatory markers and either of the depression subscales in the regularized networks. There was an edge between *TNF-a* and *Somatic depression* in 1A (Unregularized), which was negative, meaning higher levels of *TNF-a* were associated with a lower severity of *Somatic depression* and vice versa, and although this association was below the threshold in 1A (CV) to present as an edge, this association (*TNF-a—Somatic depression*) was recovered in 53% of bootstrap resamples in 1A (CV). This negative association could have been driven by *Gender*, as *Gender* was associated with both *TNF-a* and *Somatic depression* (see 6.3.3 Indirect associations between inflammatory biomarkers and depression below). A positive association between *IL-6* and *Psychological depression* was also recovered in over 50% of bootstrapped resamples in 1A (Unregularized). However, neither of these associations (*TNF-a—Somatic depression* and *IL-6—Psychological depression*) survived covariate adjustment; that is, they did not present as an edge, and they were recovered in under 50% of bootstrap resamples in 1B (CV) and 1B (Unregularized) (PIRs <50%). See Table 14 for edge weights and PIRs of direct associations between inflammatory markers and depression subscales and Appendix C for the network graphs of 1A and 1B (Fig C-1).

6.3.2. Direct associations between Inflammatory Biomarkers and Individual Depression Symptoms

The edge between *CRP* and *Loss of libido* was the most consistent direct association across the symptom networks. This edge was present in most of the networks regularized with CV (2CM (CV), 2CLM (CV), 2DC (CV), 2DL (CV), and 2DLM (CV); see Figs 9, 10, and 11), and in all the unregularized networks, pre and post covariate adjustment. Additionally, although the association *CRP-Loss of libido* did not meet the threshold in 2CC (CV), 2CL (CV), or 2DM (CV) to present as an edge in these networks, it was non-zero in over 50% of bootstrapped resamples in these networks, with PIRs of 66%, 59%, and 59%, respectively.

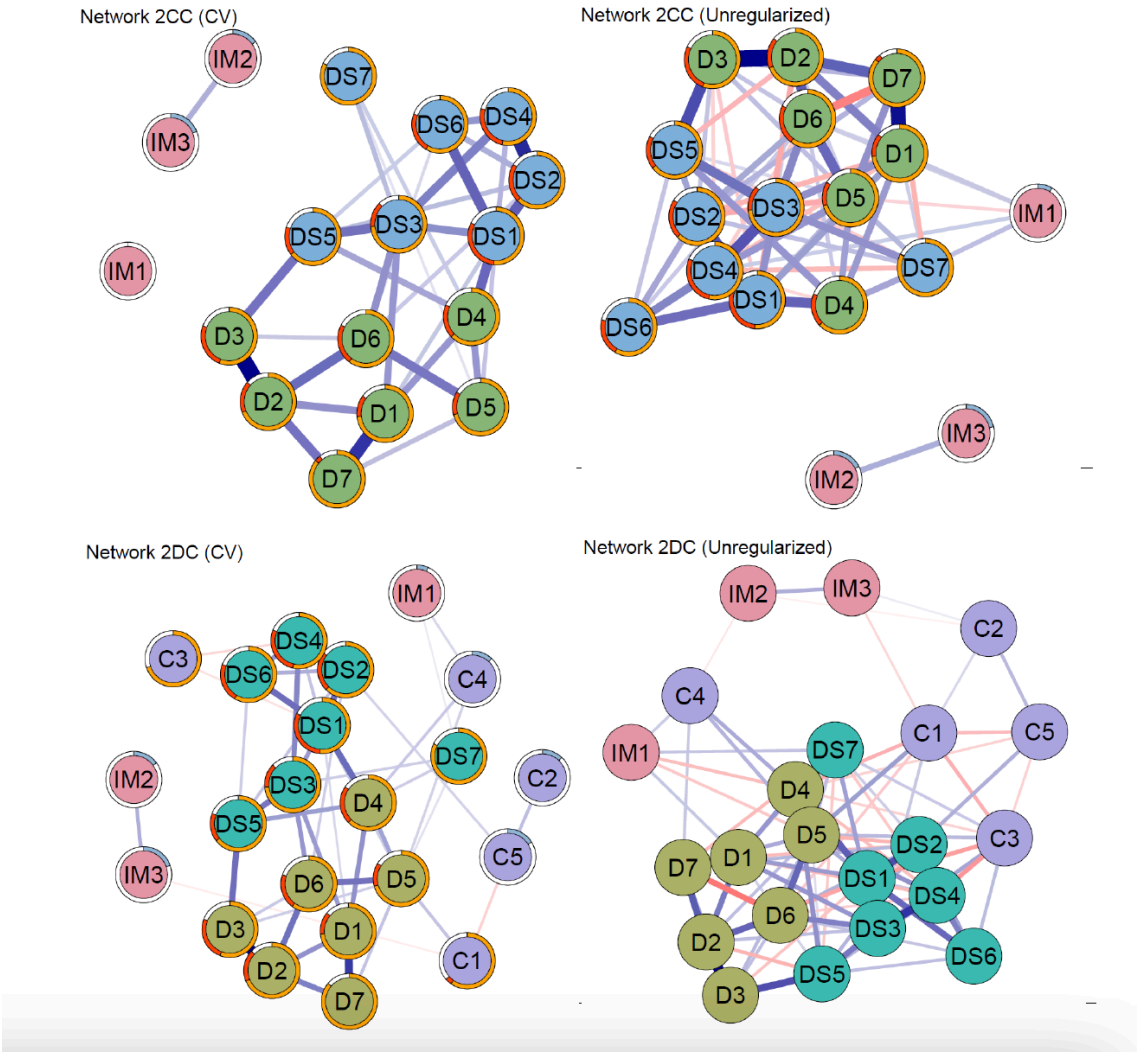

Figure 8 Networks 2CC (CV), 2CC (Unregularized), 2DC (CV), and 2DC (Unregularized)

Legend: D1=Sadness, D2=Pessimism, D3=Past failure, D4=Loss of pleasure, D5=Self-dislike, D6=Self-criticalness, D7=Suicidal thoughts, DS1=Loss of energy, DS2=Sleep disturbance (presence/absence), DS3=Irritability, DS4=Appetite disturbance (presence/absence), DS5=Concentration difficulties, DS6=Fatigue, DS7=Loss of libido, IM1=CRP, IM2=IL-6, IM3=TNF-a, C1=Gender, C2=Smoking, C3=Exercise, C4=BMI, C5=Alcohol.

There were no associations between any inflammatory markers and *Appetite disturbance* when it was measured as a composite symptom or for *Decreased appetite* (all 2CC and 2CL networks; see Figs 8 and 10) or the level denoting 'decreased appetite' in *Appetite disturbance 3-level.* There were positive associations, however, between *CRP* with *Increased appetite* (2CM (Unregularized) and 2DM (Unregularized); see Fig 9); and with *Appetite disturbance 3-level*, between *CRP* and the level representing increased appetite (2CLM (CV), 2CLM (Unregularized), 2DLM (CV), and 2DLM (Unregularized); see Fig 11). Although there was no edge between *CRP* and *Increased appetite* in the networks 2CM (CV) or 2DM (CV), this edge

was non-zero in over 50% of bootstrap resamples, with PIRs of 51% in both cases. Adding covariates to the networks affected most of the associations between *CRP* and the symptoms related to increased appetite and libido loss minimally, with the exception of the regularized network 2DM (CV), where the edge was lost between *CRP* and *Loss of libido* but was recovered in over 50% of bootstrap resamples (PIR = 59%). Overall, adjusting for covariates affected the edge weights of the associations between *CRP* with symptoms related to increased appetite and libido loss very little, with the main impact being small reductions in some of the PIRs for the edge *CRP—Loss of libido.*

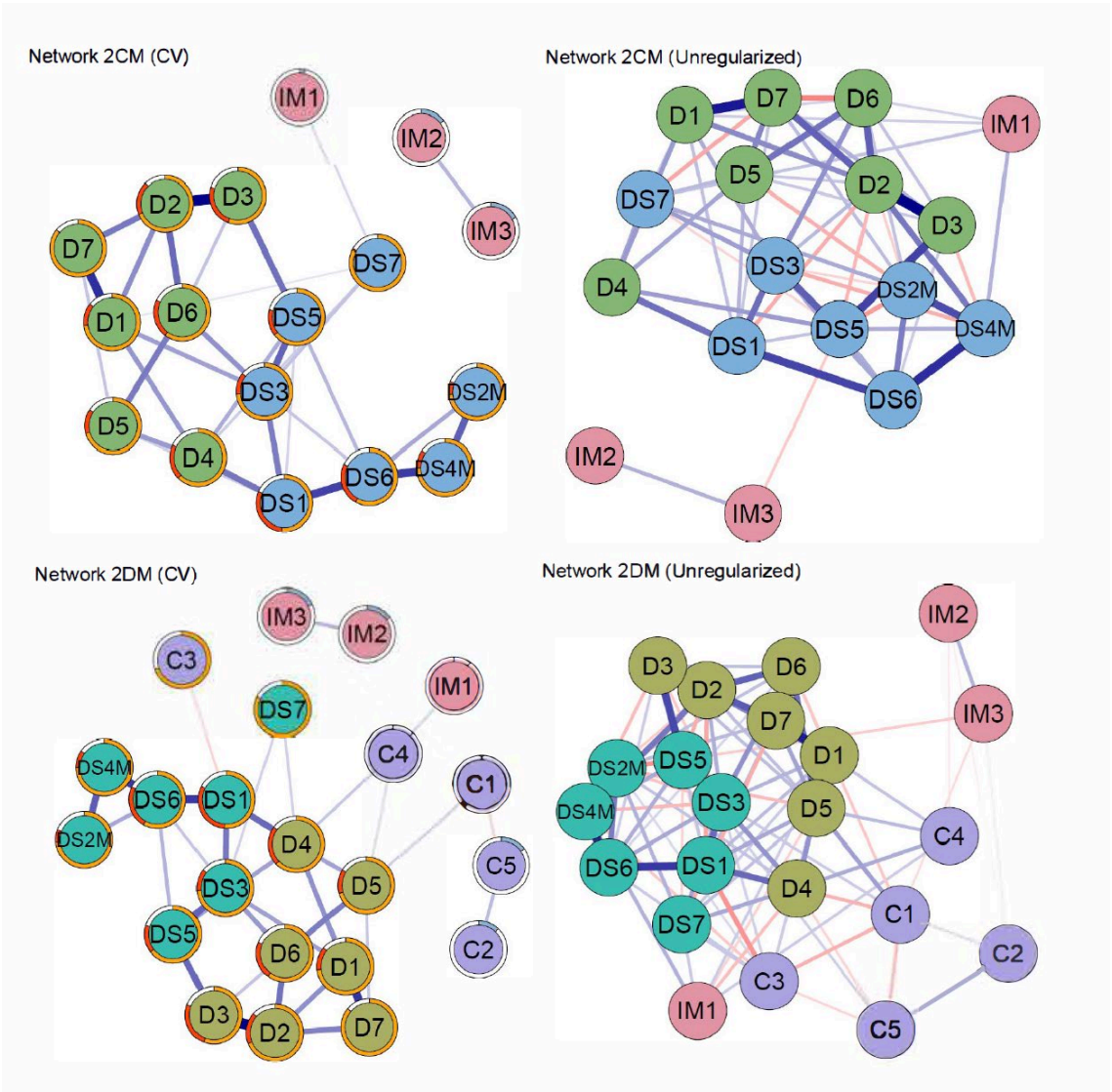

Figure 9 Networks 2CM (CV), 2CM (Unregularized), 2DM(CV) and 2DM (Unregularized)

Legend: D1=Sadness, D2=Pessimism, D3=Past failure, D4=Loss of pleasure, D5=Self-dislike, D6=Self-criticalness, D7=Suicidal thoughts, DS1=Loss of energy, DS2M= Increased sleep, DS3=Irritability, DS4=Increased appetite, DS5=Concentration difficulties, DS6=Fatigue, DS7=Loss of libido, IM1=CRP, IM2=IL-6, IM3=TNF-a, C1=Gender, C2=Smoking, C3=Exercise, C4=BMI, C5=Alcohol.

Other weaker associations in the networks included a negative association between *TNF-a* with *Concentration difficulties*, meaning lower *TNF-a* scores were associated with having concentration difficulties (2CM (Unregularized), 2CL (EBIC), 2CL (CV), and 2CL (Unregularized); see Figs 9 and 10), but the edge did not survive covariate adjustment. In all the unregularized networks with covariates (2DC, 2DM, 2DL, and 2DLM), *CRP* was negatively associated with *Loss of pleasure*, and also negatively with *Self-dislike* in 2DC (Unregularized) and 2DL (Unregularized), but neither of these associations were reliably present in any of the networks without covariates (2CC, 2CM, 2CL, or 2CLM). The negative associations between *CRP* with *Loss of pleasure* and *Self-dislike* could have been the result of *BMI,* which was positively associated with *CRP* and with both these symptoms (see section 6.3.3 below Indirect associations between inflammatory biomarkers and individual depression symptoms below). There were no direct associations between *IL-6* and any depression symptoms. See Table 14 for edge weights and PIRs of direct associations between inflammatory markers and depression symptoms.

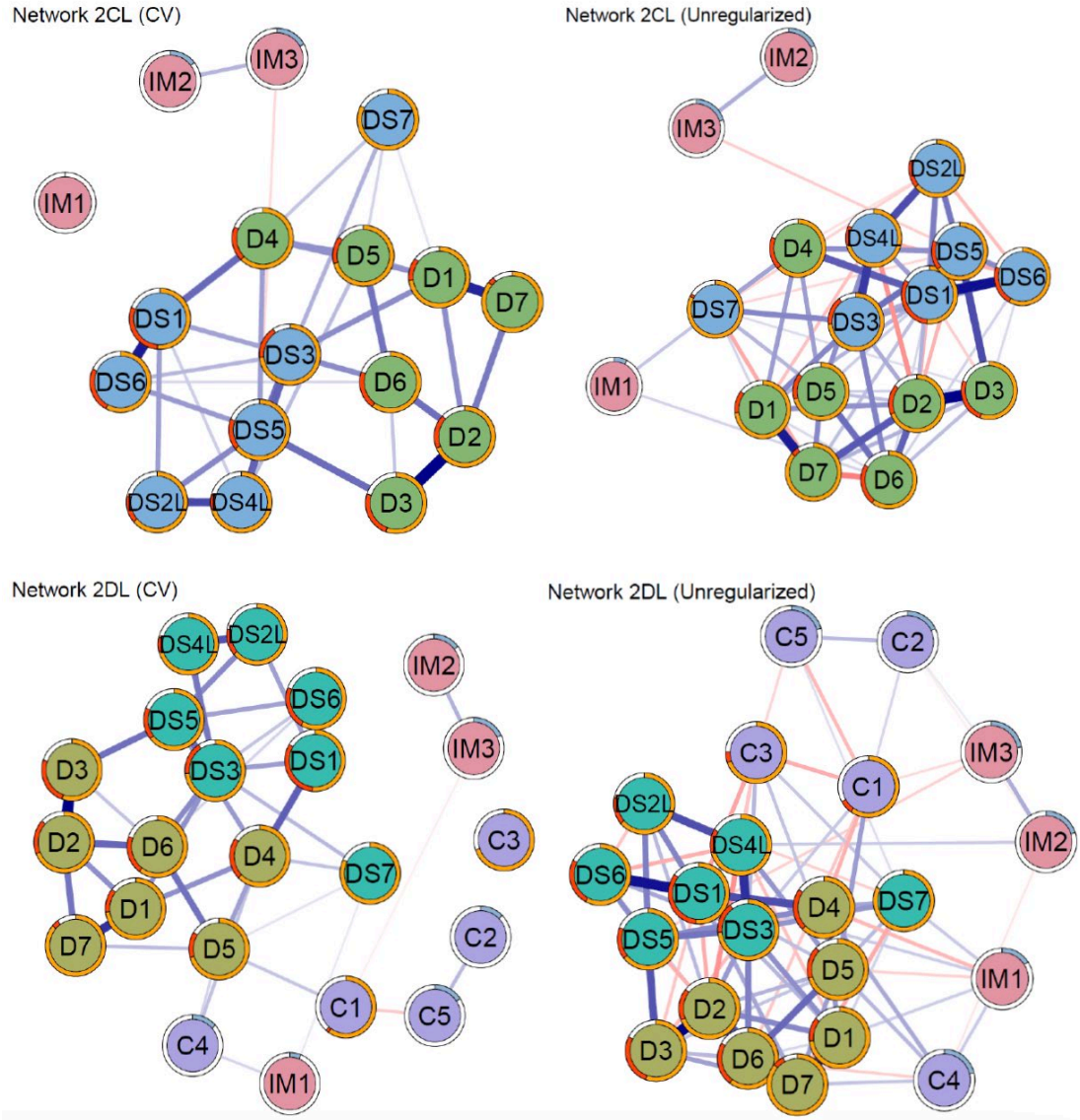

Figure 10 Networks 2CL (CV), 2CL (Unregularized), 2DL(CV) and 2DL (Unregularized)

Legend: D1=Sadness, D2=Pessimism, D3=Past failure, D4=Loss of pleasure, D5=Self-dislike, D6=Self-criticalness, D7=Suicidal thoughts, DS1=Loss of energy, DS2L= Decreased sleep, DS3=Irritability, DS4L=Decreased appetite, DS5=Concentration difficulties, DS6=Fatigue, DS7=Loss of libido, IM1=CRP, IM2=IL-6, IM3=TNF-a, C1=Gender, C2=Smoking, C3=Exercise, C4=BMI, C5=Alcohol.

Table 14 Edge weights/ Probability Inclusion Rates (PIRs) of direct associations between inflammatory biomarkers and depression measures

Networks[a] with depression subscales	Inflam-matory biomarker	Psycho-logical depression	Somatic depression			
1A (EBIC)	None	x	x			
1A (CV)	TNF-a	x	0/53%			
1A (Unreg)	TNF-a	x	-0.10/66%			
1A (Unreg)	IL-6	0/54%	x			
1B (EBIC)	None	x	x			
1B (CV)	None	x	x			
1B (Unreg)	None	x	x			
Networks[a] with individual depression symptoms	Inflam-matory biomarker	Loss of pleasure	Self-dislike	Appetite	Concen-tration difficulties	Loss of Libido
2CC[b] (EBIC)	None	x	x	x	x	X
2CC (CV)	CRP	x	x	x	x	0/66%
2CC (Unreg)	CRP	x	x	x	x	0.31/77%
2CM[c] (EBIC)	None	x	x	x	x	X
2CM (CV)	CRP	x	x	0/51%	x	0.15 /66%
2CM (Unreg)	CRP	x	x	0.39/66%	x	0.31 /74%
2CM (Unreg)	TNF-a	x	x	x	-0.26/51%	X
2CL[d] (EBIC)	TNF-a	x	x	x	-0.15/34%	X
2CL (CV)	CRP	x	x	x	x	0/59%
2CL (CV)	TNF-a	x	x	x	-0.15/43%	X
2CL (Unreg)	CRP	x	x	x	x	0.29/70%
2CL (Unreg)	TNF-a	x	x	x	-0.23/51%	X
2CLM[e] (EBIC)	None	x	x	x	x	X
2CLM (CV)	CRP	x	x	0.08/68%	x	0.14/61%
2CLM (Unreg)	CRP	x	x	0.22/82%	x	0.31/62%

2DC[b] (EBIC)	None	x	x	x	x	X
2DC (CV)	CRP	x	x	x	x	0.08/66%
2DC (Unreg)	CRP	-0.33/67%	-0.28/60%	x	x	0.29/66%
2DM[c] (EBIC)	None	x	x	x	x	X
2DM (CV)	CRP	x	x	0/51%	x	0/59%
2DM (Unreg)	CRP	-0.33/69%	x	0.41/65%	x	0.29/62%
2DL[d] (EBIC)	None	x	x	x	x	X
2DL (CV)	CRP	x	x	x	x	0.08 / 59%
2DL (Unreg)	CRP	-0.36/67%	-0.23/51%	x	x	0.27/58%
2DLM[e] (EBIC)	None	x	x	x	x	X
2DLM (CV)	CRP	x	x	0.08/65%	x	0.15/56%
2DLM (Unreg)	CRP	-0.33/51%	x	0.22/75%	x	0.29/51%

Note x = no associations between inflammatory biomarker(s) and depression measure.

[a] All networks beginning with 2C were unadjusted, and those beginning with 2D were adjusted for Gender, Smoking, Exercise, BMI, and Alcohol.

[b]In all 2CC and 2DC networks, symptoms related to sleep and appetite disturbances were measured as composite symptoms, Sleep disturbance and Appetite disturbance.

[c] In all 2CM and 2DM networks, symptoms related to sleep and appetite disturbances were measured in terms of Increased sleep and Increased Appetite.

[d] In all 2CL AND 2DL networks, symptoms related to sleep and appetite disturbances were measured in terms of Decreased sleep and Decreased Appetite.

[e] In all 2CLM and 2DLM networks, symptoms related to sleep and appetite disturbances were measured as 3-Sleep disturbance 3-level (none / less / more) and Appetite disturbance 3-level (none / less / more).

6.3.3. Indirect Associations between Inflammatory Biomarkers and Depression Subscales

Higher *CRP* was indirectly associated with *Psychological depression* through *BMI* in networks 1B (CV) and 1B (Unregularized), as higher *BMI* was associated with higher *CRP*, in all networks including 1B (EBIC), and higher *BMI* was also associated with higher severity of *Psychological depression*, in 1B (CV) and 1B (Unregularized). In 1B (CV), there was no edge between *BMI—Psychological depression*, but it was recovered in 68% of bootstrapped resamples. This indirect association between *CRP* and *Psychological depression* through BMI was the most reliable indirect association in the depression subscale networks, based on edge weights and PIRs. Higher *BMI* was also more weakly associated with higher levels of *TNF-a*

and lower levels of *IL-6* in 1B (CV) and 1B (Unregularized), and with lower scores for *Somatic depression* in 1B (Unregularized), with PIRs >50% in all cases.

TNF-a was indirectly associated with *Somatic depression* through *Gender* in 1B (Unregularized), as *TNF-a* was negatively associated with *Gender*, indicating that females had lower *TNF-a* than males, and *Gender* was positively associated with *Somatic depression*, indicating that females had higher *Somatic depression* severity than males, on average. A positive association between *Gender* and *Psychological depression* was recovered in over 50% of bootstrapped resamples in 1B (Unregularized), but this was less robust than the association with *Somatic depression*. There was no evidence that *BMI* or *Gender* moderated these relationships, based on the results of moderated network analysis.

6.3.4. Indirect Associations between Inflammatory Biomarkers and Individual Depression Symptoms

Higher *CRP* was indirectly associated with the symptom *Loss of pleasure* through *BMI* in all the covariate networks, including those regularized with EBIC (all 2DC, 2DM, 2DL, and 2DLM networks), and this was the most robust indirect association between inflammatory markers and depression symptoms, based on edge weights and PIRs. Higher *CRP* was also indirectly associated with *Self-dislike* through *BMI* in all covariate networks regularized with CV, all unregularized networks, and in 2DC (EBIC). The nature of the direct and indirect relationships between *CRP* with these symptoms varied, with the direct relationship between *CRP* and these symptoms being negative (see section 6.3.2 Direct Associations between Inflammatory Biomarkers and Individual Depression Symptoms above), and the indirect relationship being positive, as higher *CRP* was associated with higher *BMI* and higher *BMI* with *Loss of pleasure* and *Self-dislike* prevalence (Figs 8 to 11). The direct negative associations between *CRP* with *Loss of pleasure* and *Self-dislike* were only present in the unregularized networks that included covariates, and the indirect associations between *CRP* with these symptoms through *BMI* were much stronger and more robust, particularly the edge *BMI—Loss of pleasure*. One possible explanation for the negative associations between *CRP* and these symptoms is that *BMI* was exerting a suppressor effect; another possibility is that the negative direct associations were the result of positive confounding by *BMI*. The positive association between *CRP* and *BMI* was one of the strongest across all networks.

In most of the covariate networks regularized with CV, *TNF-a* was indirectly associated with *Self-dislike* through *Gender*, as *TNF-a* was negatively associated with *Gender*, showing that females had lower *TNF-a* than males on average, and *Gender* was positively associated with *Self-dislike*, indicating that females had a higher prevalence of this symptom than males. This indirect association was also present in the covariate unregularized networks, but reliability for the edge between *TNF-a* and *Gender* was below the threshold, with PIRs < 50%. There was no

evidence that *BMI* or *Gender* moderated these indirect relationships, based on the results of moderated network analysis.

In all the networks which measured symptoms related to sleep and appetite as disaggregated symptoms (networks 2CM, 2DM, 2CL, and 2DL), *Increased appetite* was strongly and robustly associated with *Increased sleep* (Fig 9). Similarly, in the networks where sleep and appetite were measured as 3-level categorical variables, the level measuring increased sleep was strongly associated with the level measuring increased appetite, but there were no associations between the levels increased sleep and decreased appetite, or vice versa (Fig 11). This meant that measures for increased sleep were indirectly associated with *CRP* through their positive associations with measures for increased appetite. The other strongest and most robust indirect association between *CRP* and depression symptoms was with *Fatigue* through measures related to increased appetite.

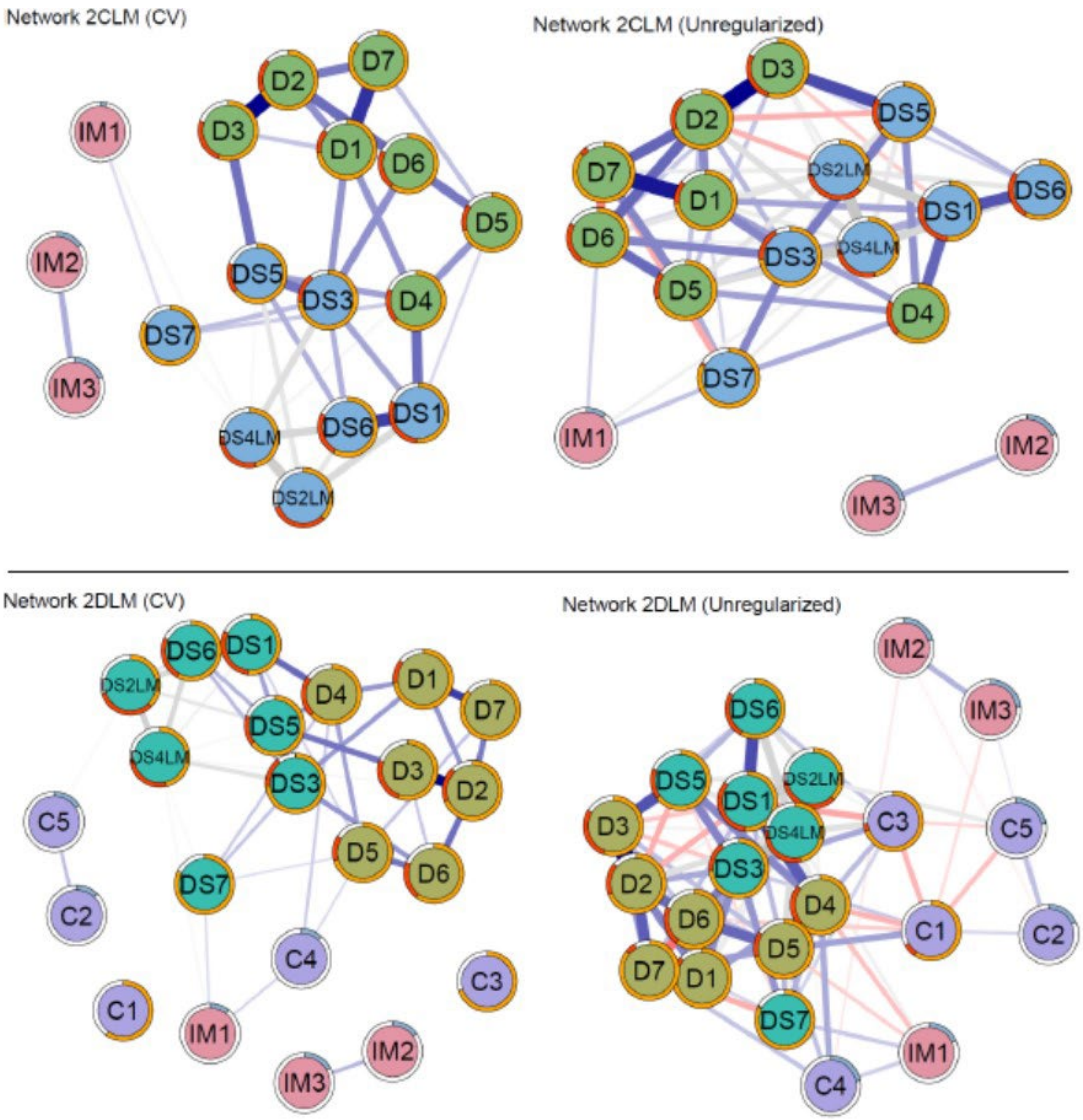

Figure 11 Networks 2CLM (CV), 2CLM (Unregularized), 2DLM (CV) and 2DLM (Unregularized)

Legend: D1=Sadness, D2=Pessimism, D3=Past failure, D4=Loss of pleasure, D5=Self-dislike, D6=Self-criticalness, D7=Suicidal thoughts, DS1=Loss of energy, DS2LM=Sleep disturbance 3 Level (None/less/more) DS3=Irritability, DS4LM=Appetite disturbance 3 Level (None/less/more) DS5=Concentration difficulties, DS6=Fatigue, DS7=Loss of libido, IM1=CRP, IM2=IL-6, IM3=TNF-a, C1=Gender, C2=Smoking, C3=Exercise, C4=BMI, C5=Alcohol.

6.3.5. Individual Depression Symptom Networks – Predictability and Centrality

Strength centrality stability, based on CS-coefficients, was above the threshold of 0.25 for all the networks, but Degree centrality stability fell below 0.25 in 2CM (CV), 2CM (Unregularized), 2DM (Unregularized), 2DL (Unregularized), 2CLM (CV), 2CLM (Unregularized), and 2DLM (Unregularized), and therefore the results for Degree centrality for these networks were excluded from the analysis. The predictability could not be displayed visually in the unregularized networks of 2DC, 2CM, and 2DM, as the normalised accuracy for one node was less than zero (below the intercept model).

Overall, *Loss of energy* had the highest node influence across the networks, based on predictability statistics and centrality metrics. It had the highest predictability in every network except for 2CLM and 2DLM, where *Sleep disturbance 3-level* had the highest predictability, followed by *Loss of energy*, but the high predictability of *Sleep disturbance 3-level* in these networks was largely due to the high correlations between the levels of increased sleep with increased appetite and between decreased sleep with decreased appetite. The nodes with the highest Strength and Degree centralities, and that were estimated with sufficient stability based on CS-coefficients, were *Loss of energy* and *Irritability*.

See Appendix C, Table C-2 for details of the results of the bootstrapped resamples and Table C-3 for the predictability statistics and centrality metrics.

6.4. Discussion

The aim of the present study was to test the hypotheses that associations between inflammatory markers and depression symptoms would be symptom specific, more likely for the physical symptoms of depression that map to the somatic scale, and most likely for those symptoms related to increased appetite, fatigue, and hypersomnia, that also characterise atypical depression. Our hypotheses were largely supported in terms somatic symptom associations, as only the symptom constructs for libido loss and increased appetite were consistently and reliably associated with *CRP*, and both these symptoms map to the somatic dimension of depression in the inventory used, BDI-II (Beck, 1996). The findings partially support the hypothesis that symptoms characteristic of atypical depression would be most likely to be associated with inflammation, as increased appetite (in the context of depression) is a discriminant feature of atypical depression (Lamers et al., 2012; Lamers et al., 2013).

The findings support previous research that found associations between raised levels of inflammatory markers (including CRP) with increased appetite in depression (Lamers et al., 2018; Milaneschi et al., 2021; Simmons et al., 2020) and partially endorse those that found

associations with the atypical depression subtype (Hickman et al., 2014; Lamers et al., 2013). Although no symptoms related to hypersomnia or fatigue (other atypical depression symptoms) were directly associated with any inflammatory markers, the symptom constructs for increased appetite, hypersomnia (increased sleep), and fatigue were all closely connected in networks which measured sleep and appetite as disaggregated symptoms. The findings also provide some evidence for the existence of a depression phenotype, typified by higher inflammatory and metabolic markers, such as CRP and BMI, and accompanied by appetite increases (Milaneschi et al., 2020; Simmons et al., 2020); although in the current study there were no associations between *BMI* and measures of appetite increases, contrasting with other studies (Lamers et al., 2018; Milaneschi et al., 2021; Milaneschi et al., 2017). The current study does not provide evidence that decreased appetite or general appetite disturbances are linked to inflammation as these were not associated in any of the networks; and there were no reliable associations between *IL-6* or *TNF-a* and any depression subscales or individual symptoms.

In the studies by Moriarity et al. (2021) and Lee et al. (2023), the symptoms relating to appetite disturbances were associated with CRP, pre and post full covariate adjustment, but in Fried et al. (2020), the edge between CRP and appetite disturbance disappeared after full covariate adjustment. In all these studies, appetite disturbances were measured as composite symptoms (with increases and decreases combined), meaning detail about the nature of the association (increased or decreased appetite) could not be discerned and both Moriarity et al. (2021) and Fried et al. (2020) cited this as a study limitation. Separating out appetite disturbance into increased or decreased in depression inventories or clinical interviews has the potential to enhance our understanding of how appetite changes may be dividing depressed groups immunologically and have implications for treatment plans. There is a growing body of evidence suggesting that there may be divergent associations between inflammatory markers and appetite changes, depending on the nature of the disturbance (Lamers et al., 2018; Lamers et al., 2013; Milaneschi et al., 2021; Simmons et al., 2016; Simmons et al., 2020) .

Associations between CRP and depression measures have been lost or severely attenuated after adjusting for lifestyle and health factors, and in particular BMI, in a number of studies (Duivis et al., 2013; Fried et al., 2020; Lamers et al., 2013; Liu et al., 2014; Milaneschi et al., 2021) but had minimal effect on these relationships in the current study. The strong associations between inflammatory markers, measures of metabolic dysregulation (such as BMI, waist circumference, and insulin), and increased appetite in previous studies have provided evidence that these associations may be a core characteristic of a depression phenotype, IMD, typified by immune and metabolic dysregulation (Milaneschi et al., 2020; Simmons et al., 2020). In the present study, *BMI* was robustly associated with *CRP* but not measures of increased appetite. The absence of an association in the present study between *BMI* and measures of increased appetite

indicate that the role of BMI in these relationships is complex and varied, as has been shown elsewhere (Chiang et al., 2017; Duivis et al., 2013). Liu et al. (2014) found the association between CRP and depression remained significant after adjusting for BMI amongst men, but not women. In the present study, this lack of a direct association between *BMI* and *Increased appetite* could be due to the characteristics of the study sample. Duivis et al. (2013), Lamers et al. (2013) and Milaneschi et al. (2021) all used samples from a Dutch longitudinal study, NESDA, where participants were predominantly Dutch and White (Penninx et al., 2008.). Research with another European cohort has found strong links between atypical depression, which is characterized by appetite increases, and obsesity (Lasserre et al., 2014). The sample in the present study differed socio-demographically, in terms of age (mean age of around 20 in the current study, with little variation (age range 19-20)) compared to mean ages of over 40 with wide variation (age ranges 18-65) in these other studies), ethnicity and culture (all of Pacific Island heritage and living in NZ compared to predominantly white and European); and average *BMI* (33kg/m^2 compared to around 25-26 kg/ m^2). Additionally, in the present study no other markers of metabolic syndrome, other than *BMI*, were included. These factors could potentially affect such associations, and more research is needed on the nature of the relationships between CRP, depression, and BMI, to investigate the contribution of different metabolic factors to inflammation-appetite associations, and more broadly inflammation-depression links, for differing levels of BMI, life stages and ethnicities.

The association between *CRP* and *Loss of libido* is not widely reported, and this is likely because this symptom is rarely included in analyses at the symptom-item level. Two exceptions include Fried et al. (2020), which did not find any associations between loss of libido with inflammatory markers, and a study by van Eeden et al. (2020) which did. These differences in findings are unlikely to be due to the nature of the sample as both studies (Fried et al., 2020; van Eeden et al., 2020) used baseline data from the same cohort (NESDA), with small variations in final analytic samples. These variations in outcomes may be related to the statistical methodologies used, the way inflammation was measured, or the covariates adjusted for, which all differed. However, the current study used the same methods as Fried et al. (2020) and therefore the association between *CRP* and *Loss of libido* was independent of any procedural variations. The strong association found in the present study between *CRP* and *Loss of libido* suggests that the symptom should be included in future studies investigating associations between inflammation and depression, particularly should the sample consist of young adults.

Loss of libido can be classed as a symptom of anhedonia (Cogan et al., 2023; Solibieda et al., 2023) and, through its mapping to the anhedonia scale, this finding is consistent with other research that has found links between inflammation and anhedonia (Felger et al., 2016), including with depressed adolescents (Rengasamy et al., 2021) and adolescents with a diverse

range of mental disorders (Freed et al., 2018). Symptoms of anhedonia have been linked to dopamine dysfunction (Felger, 2017), as has appetite control and overeating (Mills et al., 2020; Wang et al., 2001), although the results relating to appetite control have been mixed as another study found no associations between reduced dopamine function and compensatory over-eating (Hardman et al., 2012). A recently published study found that a drug that increased dopamine in the brain led to improvements in reward circuitry (which correlated with decreases in symptoms related to anhedonia) in depressed individuals with raised levels of CRP (defined in this study as >2 mg/L), but not those depressed individuals with unheightened levels (CRP <= 2 mg/L) (Bekhbat, Li, et al., 2022; Felger, 2023). This indicates that individuals with both inflammation and depression may benefit from medications that raise dopamine levels and that more investigation into the impact of inflammation-associated dopamine dysregulation could benefit those who exhibit both inflammation and depression (Felger & Miller, 2012), in particular those presenting with symptoms related to anhedonia (Bekhbat, Li, et al., 2022; Felger, 2023). Majd et al. (2020) suggest that clustering symptoms by brain regions known to be associated with them could be used to inform treatment plans. Gut health has also been associated with inflammation, dopamine (Franco et al., 2021), symptoms of depression (Barandouzi et al., 2020; Jacka, 2017), sexual dysfunction (Falk et al., 2018), and appetite regulation (Murphy & Bloom, 2004); and the beneficial impact of improving gut health on depression has been documented (Methiwala et al., 2021). Targeting treatment strategies towards dopamine regulation and improving gut health may help break the reinforcing feedback loops between depression and inflammation that exist for certain groups of depressed people, and which make their depression harder to treat.

There was evidence that *BMI* may have been acting as a suppressor variable or positive confounder on the relationships between *CRP* with *Loss of pleasure* and *Self-dislike*, as the negative association between *CRP* with both these symptoms was only present in the networks with covariates, and *BMI* was positively associated with *CRP*, *Loss of pleasure*, and *Self-dislike* (for more on positive confounding and suppression effect see (MacKinnon et al., 2000)). Overall, the indirect positive associations of *CRP* with *Loss of Pleasure* and *Self-dislike* via *BMI* were much more reliable than the direct negative associations between *CRP* and these symptoms. *BMI* may play a potential causal role in the relationships with *Loss of pleasure* and *Self-dislike*, as suggested elsewhere between BMI and anhedonia (Kappelmann, Arloth, et al., 2021) or be in a self-reinforcing feedback loop with these symptoms, although causality of any associations was not possible in the current cross-sectional study. BMI has been found to moderate (Chiang et al., 2017) and mediate (Duivis et al., 2013) the relationship between inflammation and depression in different studies. The findings in the present study reinforce the complexity of these relationships and the fact that the role that BMI plays may differ, depending on the nature of the sample, including BMI levels. The role of BMI in associations between depression symptoms and inflammation warrants more investigation cross-sectionally and

longitudinally, as few studies have examined this relationship from a temporal perspective, whilst also measuring depression in terms of individual symptoms.

There were no direct associations between any inflammatory markers and the symptom constructs related to sleep, energy levels, or fatigue in the current study, which is consistent with Lee et al. (2023), but not Moriarity et al. (2021) or Fried et al. (2020). Moriarity et al. (2021) found evidence of an association between CRP and fatigue, which was slightly less robust than between CRP and appetite (PIRs of 67% and 81%, respectively in the covariate adjusted unregularized network) and Fried et al. (2020) found associations between all inflammatory markers (CRP, IL-6, and TNF-a) with both insomnia and hypersomnia. In the current study, symptom measures for increased sleep and fatigue were indirectly associated with *CRP*, however, through symptom measures for increased appetite, and the symptom *Loss of energy* was overall the most influential node across the networks (see Appendix C, Table C-3). Targeting treatment strategies at highly connected symptoms, such as *Loss of energy* or *Irritability* (which also had high centrality scores in the present study), has the potential to have a wider impact by affecting all connected symptoms and could help break debilitating feedback cycles (Borsboom, 2017).

There were no reliable associations between any of the inflammatory markers and individual depression symptoms in the network models regularized with EBIC. These findings concur with the two network studies that used regularization with EBIC to estimate depression symptom networks (Fried et al., 2020; Moriarity et al., 2021), where criterion associations (between individual depression symptoms and inflammatory markers) became non-significance in the networks regularized with EBIC, after adjusting for all covariates[28]. However, in Moriarity et al. (2021) in the networks which included participants with CRP > 10mg/L the associations between CRP with Fatigue and appetite remained after full covariate adjustment but were weak and with PIRs of 38% and 58%, respectively. Regularization with EBIC may be inappropriate for some network analyses (Williams et al., 2019), particularly if the network analyses includes variables from differing planes, as these associations tend to be weaker than those between variables from the same plane and so have a higher risk of being shrunk to zero (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021), as regularization with EBIC favours more parsimonious models. However, this study also investigated a third way and included regularization using CV, a method with higher sensitivity than EBIC (Wysocki & Rhemtulla,

[28] In Fried et al. (2020), in the conceptual replication of Jokela et al. (2016), CRP was associate with 'sleep problems' and 'energy levels' in the network regularized with EBIC, after adjusting for age and sex. This network modelled associations between CRP and 9 constructs related to DSM Depression criteria. In the regularized full network model, which included 28 depression symptoms and full covariate adjustment, there were no associations between inflammatory markers and depression symptoms.

2021). The findings from the networks estimated using regularization with CV were more similar to the networks estimated without regularization than to those estimated using regularization with EBIC, when the PIR rates of the unregularized networks were taken into account. The appropriateness of different methods depends largely on the objectives of research and whether the aims are more tuned to discovery or accuracy.

6.5. Strengths and Limitations

This study had several strengths. Primarily, it disaggregated symptoms related to sleep and appetite into increased and decreased, so the direction of any associations could be established. It was the first study to investigate associations between inflammation and depression in Pacific New Zealanders. The sample was homogeneous with respect to age, ethnicity, and location (all were Auckland based) reducing the potential for misleading results based on socio-demographic heterogeneity; and as it was from a birth cohort, it is likely to be representative of the selected population. It was a procedural replication of three recent network studies and so helped to address challenges around the replicability of psychological network analysis (Forbes et al., 2017) and the cohort was younger on average than those in the network studies it was replicating, allowing for cross-cultural, cross-ethnic, and cross-age comparisons. It also had limitations, the main one being its cross-sectional design, which meant that causality could not be established. Data on other mental disorders, such as anxiety spectrum disorder and post traumatic disorder, were not included in this study, and the psychological data and most of the covariate data were self-reported. Depression is often comorbid with other mental and physical health conditions (Mimura, 2001), and it is possible that the associations with depression found in this study could be the result of such comorbidity. The homogeneity of the sample means it may not generalize to other populations. Finally, most of the data was collected throughout 2020, during the COVID-19 pandemic, when the lockdown level allowed for such data and blood collection. It is not known how this may have affected findings and follow up studies with the same population are recommended to assess this.

6.6. Conclusion

The findings from the present study support the hypothesis that associations between inflammation and depression are more likely for somatic depression symptoms (see Chapter 5 and for a published review see (Majd et al., 2020), as *CRP* was associated with symptom measures related to increased appetite and libido loss, both from the somatic symptom scale. The findings partially endorse the hypothesis that criterion associations would be most likely for symptoms of atypical depression, which is characterized by appetite increases. These results corroborate those in other studies that also found associations between inflammatory markers

and increased appetite (Lamers et al., 2018; Milaneschi et al., 2021; Simmons et al., 2020), despite the age and ethnic differences in these studies compared to the present study. The results provide some evidence for the model of immune-metabolic depression, as suggested elsewhere (Milaneschi et al., 2020; Milaneschi et al., 2017; Simmons et al., 2016; Simmons et al., 2020) as *CRP* was associated with symptom constructs for increased appetite and *BMI*, however, *BMI* was not linked to measures of increased appetite. There were no associations, between any of the inflammatory biomarkers with symptom constructs for decreased appetite or general appetite disturbance, measured in terms of a composite symptom and the findings demonstrate the importance of disaggregating depression symptoms related to appetite (and also sleep based on the strong connections between the symptoms of appetite and sleep), into increased and decreased. This is fundamental if we are to progress our understanding of what links depression and inflammation and to better target treatments at the subgroup that suffer both. The association between *CRP* and *Loss of libido*, is a less commonly reported finding and future research should include it in investigations into inflammation and depression, particularly with younger adult cohorts, to test the replicability of these results. Symptoms of anhedonia and appetite dysregulation have both been linked to dopamine dysregulation (Felger, 2017; Mills et al., 2020), and the findings support more research into the beneficial effects of improving dopamine regulation and receptor pathways on depressed subgroups with inflammation, as suggested elsewhere (Bekhbat et al., 2022; Felger, 2023).

Prelude to Chapter 7

This chapter summarized the key findings, outlined how the thesis contributed to knowledge, its limitations and directions for future research.

Chapter 7. Integrated Conclusion

7.1. Overview of Thesis

The overall aim of this thesis was to apply the network approach to psychopathology, in particular to use psychological network analysis to map relationships and use the statistical tools accessible with this methodology, to gain a deeper understanding of connections between individual depression symptoms with risk factors, suicidality and inflammation amongst Pacific NZ adolescents and young adults.

To achieve these aims it answered the following specific research questions:

1. What are the risk factors for depression amongst Pacific NZ adolescents? (This question was addressed in Chapter 3).
2. What is the impact of individual depression symptoms and self-harm on suicidality for Pacific NZ adolescents? (This question was addressed in Chapter 4).
3. Are certain depression dimensions, subtypes or individual depression symptoms more likely to be associated with inflammatory markers? (This question was addressed in Chapter 5)
4. Is inflammation associated with depression in NZ Pacific young adults and what is the nature of the association? (This question was addressed in Chapter 6).

In every original study (Chapters 3, 4, and 6) and the literature review (Chapter 5) depression was measured in terms of individual symptoms, often in combination with depression measured as a single latent construct (Chapter 3) calculated by summing symptom scores or in terms of depression dimensions calculated by summing symptom subscales (Chapters 5 and 6), and the results compared with the symptom-level findings. In every original study (Chapters 3, 4, and 6) the network approach to psychopathology was applied, primarily in the fitting of network models and the use of network analysis to quantify relationships between variables or groups of variables. This network perspective was also used to gain indications of possible causal relationships. Therefore, this thesis had, three overarching aims:

1. To illustrate how measuring depression in terms of individual symptoms and applying the network framework provided detailed and nuanced information that could then be used to better inform treatment plans, therapies, and interventions.
2. Assess the extent to which direct and indirect associations, central network nodes, possible feedback loops and symptom clusters, identified in the original studies (chapters 3, 4, and 6) were potentially shaped by Pacific culture.
3. Review the theoretical implications for depression measurement, based on the findings from all chapters combined with published studies elsewhere.

In this chapter, how the thesis achieved its aims and the subsequent contributions to knowledge are discussed. These fall into five main areas:

- Revisiting the questions: practical and knowledge gap contributions
- Contribution of symptom-level analysis
- Contribution of the network approach to psychopathology
- Cultural considerations and implications
- Theoretical contributions: implications for depression measurement

7.2. Contributions to knowledge

7.2.1. Revisiting the Questions: Practical and Knowledge Gap Contributions

7.2.1.1. What are the risk factors for depression amongst Pacific NZ adolescents?

The study in Chapter 3 identified risk and protective factors for depression amongst Pacific NZ adolescents. It broke new ground in two ways. It was the first time that network analysis had been used to investigate depression with Pacific NZ adolescents, a group vulnerable to depressive symptomatology. Secondly, it was also the first network study of adolescent depression to include such a wide range of multi-dimensional potential risk factors for depression, whilst measuring depression at the symptom level. Both these facts are important as symptom level measurement alongside network analysis provides a much deeper insight into the nature of depression, with the potential for discovering symptom clusters and vicious cycles of symptoms which may reinforce each other in feedback loops, which could have implications for treatment strategies (Borsboom, 2017; Borsboom & Cramer, 2013; Fried & Nesse, 2015). Networks, with their ability to identify direct and indirect associations with targets of interest and detect influential network nodes are ideally placed to discover possible culturally shaped results. Networks have been shown to be sensitive to cultural aspects of the population being analysed (Kim et al., 2021; Osborn et al., 2020; Wasil et al., 2020). Moreover, including a wide range of risk factors reduces the probability that any connection observed between two factors in the network is spurious, that is, based on another factor that is absent from the network (Jones et al., 2017).

The study in Chapter 3 found that the main risk and protective factor for depression amongst Pacific NZ adolescents was the variable measuring the quality of the mother or main guardian relationship (*Relationship with mother*). The quality of the relationship was assessed with a self-report scale, specifically designed for adolescents, that measures three aspects of parent or peer relationships: trust, communication, and alienation (Armsden & Greenberg, 1987). Higher scores on this inventory, after reverse scoring any relevant items, indicated a better-quality relationship and were protective, and low scores a poorer quality relationship and were a risk

factor. *Relationship with mother* was strongly and reliably associated with *Depression severity* and with the largest number of symptoms, namely *Loneliness, Sadness, Self-hatred*, and *Self-criticism*. Other factors associated with *Depression severity* were lack of quality of friendships (*Not enough friends*), *Impulsivity*, *Self-assessed weight* (for the categories 'a little overweight' and 'overweight'), lack of energy (*Energy levels*), absence of School connectedness (*Part of school*), and female gender. Factors associated with at least one depression symptom, other than *Relationship with mother*, were lack of quality friendships (with symptoms *Lacking friendship* and *Self-criticism*), *Delinquency* (with symptom *Self-criticism*), *Self-assessed weight* (with symptom *Negativity towards looks*), school-connectedness (with symptom *Lacking friendship*), and spending more than seven hours a day online (with symptom *Self-hatred*).

7.2.1.2. What is the impact of individual depression symptoms and self-harm on suicidality for Pacific NZ adolescents?

The study in Chapter 4 investigated the impact of individual depression symptoms and self-harm on suicidality by fitting a series of networks: depression symptoms with suicidality; depression symptoms with self-harm and suicidality; and depression symptoms with self-harm, suicidality and a wide range of potential other risk factors. This study was the first time that associations between suicidality and depression had been investigated at the symptom item level for Pacific NZ adolescents, an under-researched and at-risk population, and the first time that network analysis had been used to investigate suicidality amongst Pacific adolescents inside or outside NZ. As described above, symptom level analysis provides important detail that can be taken forward into treatment plans, and ethnicity and culture have been shown to affect various aspects of suicidality (Christian et al., 2021; Teevale et al., 2016), which symptom level and network analysis are ideally suited to discover. This was also the first study to use network analysis to investigate the influence of self-harm and individual depression symptoms on adolescent suicidality, whilst adjusting for such a comprehensive set of possible risk factors, which as described above, reduces the risks that an association is spurious (Jones et al., 2017).

Overall, the risks that individual depression symptoms presented for *Suicidality* varied enormously, supporting the view that analysing psychopathological problems at the symptom-item level provides an in-depth insight that would not be possible with using more reductionist methods of depression measurement, such as sum scores of symptoms (Fried & Nesse, 2015a; Fried et al., 2014; McNally, 2016). *Self-harm* had the strongest association overall with *Suicidality* followed by *Pessimism.* Other symptoms linked to *Suicidality* were *Sadness* and *Negativity towards looks*. No other symptoms were associated with *Suicidality* after conditioning on other potential risk factors. The study also identified risk factors for self-harm, which as research has shown is closely linked to suicide attempts and actual suicides (Gillies et al., 2018; Hawton et al., 2012), so targeting those risk factors should also be part of any suicide prevention strategy.

7.2.1.3. Are certain depression dimensions, subtypes or individual depression symptoms more likely to be associated with inflammatory markers?

The literature review in Chapter 5 assessed the published evidence that the depression – inflammation relationship was influenced by depression dimensions, subtypes, or symptoms. There was evidence that associations between inflammatory markers and depression were more likely for CRP with somatic symptoms and for CRP those symptoms characterizing atypical depression, in particular increased appetite, hypersomnia, and fatigue/ energy related symptoms (Lamers et al., 2018; Milaneschi et al., 2021; Milaneschi et al., 2020). These findings were used to inform the hypothesis in Chapter 5.

7.2.1.4. Is inflammation associated with depression in NZ Pacific young adults and what is the nature of the association?

The study in Chapter 6 investigated associations between the most commonly studied inflammatory biomarkers (CRP, IL-6, and TNF-a) and depression, with depression measured both in terms of the two main dimensions (psychological and somatic) and individual symptoms. It tested the hypothesis that associations between depression measures and at least one inflammatory biomarker would be more for the biomarker CRP with somatic symptoms of depression and most likely between CRP and those symptoms that characterize atypical depression (hypersomnia, increased appetite, and fatigue). This study was a procedural replication of three previous network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021) investigating inflammation and depression but extended them methodologically by measuring the symptom items related to sleep and appetite as disaggregated into increased and decreased, as well as, as compound symptoms, as per these other network studies. All of these three network studies, and in fact most studies investigating associations between inflammation and somatic symptoms of depression have measured appetite disturbance as a compound symptom, whereby the nature of the disturbance (increased or decreased) was combined as one item. Two of the network studies also used a compound symptom to measure sleep disturbance (Lee et al., 2023; Moriarity et al., 2021). Disaggregating depression symptoms related to sleep and appetite is important as they can have different aetiologies (Fried et al., 2022) and have been found to have different biological profiles (Lamers et al., 2013; Milaneschi et al., 2020; Simmons et al., 2020). The study in Chapter 6 also used an additional methodology to estimate the networks, to test the extent to which statistical network methodologies were influencing findings. It was the first study to investigate associations between inflammation and depression amongst Pacific people in NZ, a group disproportionality at risk of both depression and chronic inflammatory diseases (Brewer et al., 2022; Schmidt-Busby et al., 2019). Relevant research with a wide range of ethnic and racial groups is important, as the inflammation-depression relationship may differ by race/ ethnicity (Case & Stewart, 2014; Morris et al., 2011).

The study found no associations between any inflammatory markers with either of the depression dimensions (somatic or psychological). However, when depression was measured in terms of individual symptoms, it found associations between *CRP* with *Loss of libido* and the symptom constructs for *Increased appetite*, in the unregularized networks and the networks regularized with CV. There were no reliable associations between any inflammatory markers and depression symptoms in the networks regularized with EBIC, in line with the findings from the other network studies (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021[29]). Overall, therefore, the results supported the hypothesis that associations would be most likely with symptoms from the somatic scale, as both *Increased appetite* and *Loss of libido* are on the somatic subscale for the depression instrument used, the BDI-FS (Beck et al., 2000) and partly endorsed the hypothesis that inflammation-depression associations would be most likely with atypical depression symptoms, as increased appetite is a symptom of atypical depression. When the direct and indirect associations with *CRP* were considered, all atypical symptoms included in the analysis (*Increased appetite*, hypersomnia (*Increased sleep*), and *Fatigue*) were either directly (*Increased appetite*) or indirectly (hypersomnia (*Increased sleep*), and *Fatigue*) associated with *CRP*, through *Increased appetite*. The findings also partially supported the model of immune-metabolic depression (IMD), which maps to atypical depression symptoms, in particular increased appetite, and is characterized by higher levels of CRP, higher BMI, and measures of metabolic dysregulation (Milaneschi et al., 2020; Simmons et al., 2020). The difference with this study compared to these others was that *BMI* was not directly associated with *Increased appetite*; however, *BMI* was indirectly associated with increased appetite through *CRP*.

7.3. Meta Conclusions and Contributions

7.3.1. Contribution of Symptom-level Analysis and Implications for Treatment

The contribution to the thesis objectives and so to knowledge provided by analysis at the symptom-item level can be broken down into four categories:

1. Empirical evidence that associations with risk factors, suicidality, and inflammation are highly symptom specific, and measurement of depression only in terms of a sum scores of symptoms would have obscured important information.

[29] In the study by Moriarity et al. (2021), the associations between CRP with symptoms related to appetite and fatigue did not survive full covariate adjustment with the sample that excluded participants with CRP levels of over 10mg/L, but remained as weak associations in the sample that did not exclude them.

2. Valuable detail on symptom level associations that could be used when designing interventions and treatment plans.
3. Identification of potentially culturally influenced results, which was boosted by the symptom level analysis.
4. Wider implications for depression measurement.

Points one and two above are discussed below. Point three is discussed in the section 7.3.3 Cultural considerations and implications and point four in the section 7.4 Theoretical Contributions: Implications for depression measurement**.**

7.3.1.1. Empirical Evidence for Symptom-level Measurement

In every original study and in the literature review, findings were highly symptom specific. Symptoms were differentially associated with risk factors, suicidality, and inflammation. The findings from this thesis support the view that symptoms are not interchangeable and analysis at the symptom item level provides deeper insight into various aspects of depression (Fried et al., 2014), that would not be possible with depression measurement methods that involve symptom aggregation.

In Chapter 3, risk factors for depression amongst Pacific NZ adolescents were identified, but the relationship between risk factors was highly symptom specific. Four risk factors (*Delinquency, Self-assessed weight, School connectedness*, and *Hours online*) were reliably associated with only one symptom, and the symptoms they were associated with varied in each case. *Relationship with mother* and *Relationship with friends* were the only risk factors to be associated with more than one symptom. These findings support those from two other studies, which also found differential associations between risk factors and symptoms (Fried et al., 2014; Lux & Kendler, 2010) but extends those studies by including a wider number of risk factors and modelling associations between symptoms and risk factors within a network graph. Lux and Kendler (2010) found, for example, that the risks for alcohol and substance abuse were higher for those with symptoms of guilt or suicide ideation, and that suicide ideation was associated with longer or more chronic depressive episodes. Furthermore, controlling for the depression dimensions of cognitive (often used interchangeably with psychological depression) and neuro-vegetative (often used interchangeably with somatic depression) only partly explained the heterogeneity (Lux & Kendler, 2010).

Overall, in the study in Chapter 3, there was considerable overlap between those risk factors associated with *Depression severity* and with at least one depression symptom, but with some exceptions. *Lack of energy, Gender* and *Impulsivity* were associated with *Depression severity*, but not with any depression symptoms. Conversely, *Delinquency* and *Hours online* were associated with the depression symptoms *Self-criticism* and *Self-hatred*, respectively, but not

with *Depression severity*. For *Gender* and *Lack of energy*, the lack of an association with any individual symptoms could have been due to the variance both these symptoms shared across multiple symptoms and risk factors, reducing their explanatory power. For example, in the zero order correlation matrices, *Lack of energy* was significantly associated with every depression symptom. *Gender* was associated with a large number of symptoms and risk factors, in zero-order correlation analysis. Both *Gender* and *Lack of energy* were indirectly associated with the symptoms *Lacking friendship* and *Self-criticism* through the variable measuring quality friendships, however. *Impulsivity* and *Delinquency* were strongly linked, and *Impulsivity* was indirectly associated with *Self-criticism* through *Delinquency*, and *Delinquency* was indirectly associated with *Depression severity* through *Impulsivity*. *Hours online* was not highly connected in the network, and the association with *Self-hatred* was very symptom specific. These results suggest using only sum score assessments for depression fail to capture depression's heterogeneity. However, only using symptom level analysis may also fail to detect certain risk factors. Therefore, the answer is likely to lie in using multiple measures of depression measurement, as suggested elsewhere (Fried et al., 2022).

The contribution of different depression symptoms to *Suicidality* varied substantially, with the symptom construct for *Pessimism* being the most strongly associated. As with Chapter 3, the differential impact of depression symptoms on *Suicidality* also supports the view that analysing depression as a single sum score of symptoms obscures important information and potentially hinders a more in-depth comprehension of the mental disorder or condition being investigated (Fried et al., 2014). After adjusting for a wide range of possible risk factors, the only depression symptoms associated with *Suicidality* were symptom constructs related to *Pessimism, Negativity towards looks*, and *Sadness*, with *Self-harm* followed by *Pessimism* being the strongest contributor to *Suicidality*. In line with these findings, Beck et al. (1985) found measures for hopelessness, and symptom items measuring pessimism, better predicted actual suicide than sum scores on depression inventories. The results from the studies described in Chapters 3 and 4 provide evidence for the limited usefulness of measures of depression based only on symptom aggregation, as found elsewhere (Fried & Nesse, 2014).

The literature review (Chapter 5) gave support to the theory that the inflammation-depression association may be being driven by certain symptoms of depression or depression dimensions or subtypes, with stronger evidence for associations between raised CRP with somatic depression atypical depression, and the symptoms measuring appetite, sleep, and fatigue. When appetite was disaggregated into increased and decreased, associations with higher CRP were more likely with increased appetite (Chae et al., 2022; Milaneschi et al., 2021), with some evidence for decreased appetite with IL-6 (Manfro et al., 2022; Milaneschi et al., 2021).

These symptom level associations were even more pronounced in the original study, in Chapter 6. No inflammatory markers were associated with either of the depression dimensions (psychological or somatic), but *CRP* was associated with the individual symptoms of *Loss of libido* and *Increased appetite*, fully showcasing how even when depression is measured in terms of dimensions, important associations can be obscured. In fact, this study also found that important relationships can be hidden not just by only using latent constructs based on sum scores, but also by using compound instead of disaggregated symptoms. Fried (2017) has argued against the use of compound symptoms because of the loss of important information, including in relation to associations with biomarkers. This view was supported in the study in Chapter 6. When the symptom related to appetite was measured as a compound symptom, that is where the appetite disturbances of increased or decreased were combined, there was no association between this symptom and any inflammatory biomarkers. However, when it was disaggregated into increased or decreased appetite, *Increased appetite* was positively associated with *CRP*. Most studies investigating associations between inflammatory biomarkers and symptoms have aggregated symptoms related to appetite (for a review see (Majd et al., 2020). The findings from the study in Chapter 6 strongly suggest that advancement in understanding the relationship between inflammation and depression is likely to depend, not just on symptom-level analysis, but also on using disaggregated symptoms.

7.3.1.2. Symptom Level Associations and Implications for Treatment

Symptom level analysis also provides more in-depth information that could potentially be used clinically and Fried & Nesse (2014) argue that progress in treating depression will only occur if we consider the impact of individual symptoms and their interactions. In the study in Chapter 3, for example, being in the categories of ‘a little overweight’ or ‘overweight’ of the variable self-assessed weight was weakly associated with *Depression Severity*. However, in the symptom-level analysis, the association of *Self-assessed weight* (a little overweight and overweight) with the symptom *Negativity towards looks*, was the strongest risk factor-symptom association in the symptom network. *Negativity towards looks* was also a risk factor for *Suicidality*. These findings offer a clear target for an intervention plan, based on building self-esteem, which has been shown to help to create more body positivity (O'Dea & Abraham, 2000). The strong association between spending excessive hours online and *Self-hatred* suggested that limiting online activity could benefit self-esteem and diminish self-loathing, vital targets for this age group. The outcomes from the study in Chapter 4, suggested strongly that targeting pessimism and fostering optimism may have a larger beneficial effect on suicidality than just focusing on depression overall. In the study in Chapter 6, it was symptom clusters rather than specific symptoms that indicated treatment paths, and this is dealt with in the section below on 7.3.2 Contributions of network analysis to implications for treatment.

Furthermore, as well as providing clinically relevant targets for prevention and treatment, research has found that symptoms differ in terms of their treatability (Fava et al., 2010; Uher et al., 2012) or receptiveness to certain types of treatment or interventions. One study examined associations between individual depression symptoms with social and occupational functioning in the context of psychotherapy. It sought to investigate how changes in specific symptoms, in response to psychotherapy, affected functioning. Of the nine symptoms included in the analysis, only three had a significant effect on functioning: little interest or pleasure, feeling depressed or hopeless, and feeling tired (Malkki et al., 2023). Mullarkey et al. (2020) found the impact of an internet intervention on depression was also highly symptom specific, with direct improvements on the symptoms of sadness and indecision, and indirect effects on a number of other symptoms (some aspects of insomnia, self-dislike, fatigue, anhedonia, suicidality, slowness, and agitation), with some symptoms not impacted at all. The authors advised monitoring how treatment affects depression at the symptom level, as this has been shown to be highly variable (Mullarkey et al., 2020). These discoveries also suggest that multiple types of treatment and interventions may need to be used if all relevant symptoms are to be altered.

7.3.2. Contributions of the Network Approach and Implications for Treatment

The contribution to knowledge of using the network approach had three main aspects:

1. Additional inferences made possible by using the network approach and possible consequences for treatment plans and interventions.
2. Identification of potentially culturally influenced results, which was enhanced by the network approach.
3. Wider implications for depression measurement.

Point one is discussed below, with reference to findings from the empirical studies. Point two is discussed within the section 7.3.3 Cultural considerations and implications and point four within the section 7.4 Theoretical Contributions: Implications for depression measurement.

7.3.2.1. Additional Inferences Gained by using the Network Approach and Possible Consequences for Treatment Plans and Interventions.

In this thesis the measurement of depression in terms of individual symptoms was complemented by using the network approach to psychopathology, which modelled interactions between symptoms and other variables of interest within a network graph. This enabled a number of additional insights to be drawn, by analysing the local and global topology of the network structure. Indirect as well as direct associations were easily identifiable from the network graph, which could then be tested for moderation effects (Haslbeck et al., 2019) and give indications of mediation effects. Clusters of network components may also be visually

representing feedback loops of symptoms which are reinforcing each other. According to the network approach, symptoms cluster together because of causal interactions based on direct and indirect linkages, but they may also cluster because they share characteristics or because of an underlying trait (Guyon, 2017). Network analysis provides a visual and logical explanation of these feedback loops, which have been known to exist by clinicians for decades (Beck, 1979; Ma & Teasdale, 2004). Fried & Nesse (2015a) argue that heterogeneity of depression implies that across depressed subjects there are multiple depression syndromes or conditions or phenotypes. The use of methods such as network analysis to discover the symptom clusters relevant to these conditions could be an important step in identifying them.

In every original study, indirect as well as direct network linkages were examined, as well as the detection of central nodes (Opsahl et al., 2010), nodes with the highest predictability (Haslbeck & Waldorp, 2018), and symptom clusters. Network theory argues that the additional information provided by these network tools has the potential to provide a framework for conceptualizing treatment and intervention plans (Borsboom et al., 2021). This can be by directly intervening on a node to attempt to reduce its severity, which may also impact the nodes it is connected to or by targeting an interaction between nodes, which Borsboom et al. (2021) argue may be more effective through its ability to disrupt the network. In the study in Chapter 3, for example, *Relationship with mother* was connected to the largest number of symptoms (*Loneliness, Sadness, Pessimism, and Self-hatred*). Therefore, based on network theory, if an intervention could be designed that could work to improve the mother-adolescent relationship, this may have consequential effects for the symptoms this variable was connected to (Borsboom et al., 2021), although in this study it was not known what the direction of the relationship was, as the data was cross-sectional. In the study in Chapter 4, *Negativity towards looks* was associated with *Suicidality* and *Negative peer pressure*. Based the ideas of Borsboom et al. (2021), therefore, designing an intervention that would help with body positivity when receiving negative peer pressure, or that would help withstanding up to or ignoring negative peer pressure, may break this link and also have impacts for suicidality. These interventions may require additional information about node triggers, but this could be acquired by asking people themselves about what they think may be the order of events (Frewen et al., 2013). Mobile technologies provide the potential for depressed people to record positive and negative effects in real time and within context in which they are occurring (Bringmann et al., 2013; Kramer et al., 2014). This information could then be used to fit temporal networks. Other ways network analysis could help identify treatment targets are outlined below.

In the study described in Chapter 3, school connectedness (*Part of school*) featured as a strong influencer of mental health, as feeling connected to one's school was a powerful protective factor against depression. In the symptom-level analysis, presence of school connectedness was

negatively associated with the symptom measuring lack of friendship. Presence of school connectedness was also negatively linked to school attendance, but interestingly, school connectedness was not linked to the measure for teacher rapport. These observations were detectable from the network graph and quantified using network metrics such as edge weights and illustrate the level of detail that it is possible to achieve using the network approach and network analysis. These findings also provide indications of where to target interventions. Based on network linkages. There was evidence that improvements in friendships could improve school connectedness (or vice versa, as this study was cross sectional so the direction of influence cannot be assumed), or perhaps these factors were in a bi-directional relationship. The study suggested that school connectedness has the potential to impact school attendance, through the direct connection between the two factors, although the direction of the association would need to be supported in a longitudinal study. However, it is easy to see how the links between an absence of school connectedness, lack of friendship, and poor school attendance could form a vicious downward spiral, but with the right intervention these links may have the potential to spiral in the other direction.

Similarly, the construct measuring *Impulsivity* was directly associated with the construct measuring *Delinquency* and indirectly linked to the depression symptom *Self-criticalness,* through *Delinquency*, and the node measuring *Delinquency*, was strongly associated with drug taking, gang involvement, and smoking. Past research has indicated that targeting bridging nodes may cut links with unwanted outcomes (Jones et al., 2018; Solmi et al., 2019) and so intervening to reduce impulsivity could potentially have a number of beneficial outcomes. It could reduce the risks for depression (*Impulsivity* was also associated with *Depression severity*) and the tendency to engage in delinquent behaviours (although this study was cross sectional, other studies have found that impulsivity precedes depression (Dussault et al., 2011) and delinquency (Murray & Farrington, 2010)) and cut the connection with other unwanted outcomes, such as drug taking and gang involvement. Intervening on impulsivity also has the potential to improve self-esteem due to the connection between *Delinquency* and the symptom *Self-criticism,* although this study was cross sectional so the directions of associations would need to be supported in longitudinal research.

Indirect associations may also represent targets for early interventions, particularly where there is evidence that an indirect connection could represent an earlier stage of a condition or disorder. In the study in Chapter 4, the networks showed that non-symptom risk factors for *Suicidality* were different to those for *Self-harm*, with *Suicidality* being associated with a poor-quality mother relationship, a lack of school connectedness, and substance abuse and *Self-harm* with *Negative peer pressure*, being bullied online, and being female. As there is evidence that self-harm precedes suicidality (and reinforces it) and actual suicide (Gillies et al., 2018), intervening

on risk factors for self-harm has the potential to help reduce incidences not only of self-harm, but also suicidality, with implications for future suicide attempts and actual suicides.

The study described in Chapter 6, which investigated the relationships between depression and inflammation, found that *CRP* was directly associated with *Increased appetite* and *Loss of libido,* and indirectly associated with hypersomnia and fatigue, through *Increased appetite*. Despite the fact that hypersomnia and fatigue were only indirectly linked to *CRP*, *Increased appetite*, hypersomnia and *Fatigue* were a cluster of symptoms closely connected in the network, and all were directly or indirectly associated with *CRP*. This cluster could represent a depression phenotype characterised by inflammation, metabolic dysregulation, and atypical symptoms of depression, which supports the findings of previous studies (Milaneschi et al., 2021; Milaneschi et al., 2020; Simmons et al., 2020). Identifying these symptom clusters, characterised by inflammation, has implications for therapies (perhaps involving dietary advice) and pharmacological treatments for these groups, which may include anti-inflammatories.

According to network theory, nodes with high centrality make efficacious targets for interventions based on their ability to affect many other nodes in the network (Borsboom, 2017; Borsboom & Cramer, 2013). This theory is largely untested, but Fried (2015) simulated a temporal network and showed the symptoms with the highest strength centrality did in fact trigger other symptoms. Another study found that people reporting subthreshold levels of depression with high centrality symptoms at baseline were at greater risk of developing an episode of MDD during the following six years compared to those presenting with symptoms of low centrality at baseline (Boschloo et al., 2016). Robinaugh et al. (2016) also found that central symptoms based on strength centrality did predict which symptoms were more likely to improve over time. Across the original studies in this thesis, the most central depression symptoms varied. In the study in Chapter 3, *Loneliness w*as the most central symptom followed by *Self-hatred*, based on combined measures of Strength, Closeness, and Betweenness (Opsahl et al., 2010). Therefore, aiming to reduce the severity of these symptoms may initiate what has been described as a 'a cascade of symptom deactivation' (Fried et al., 2016, p.6). Reporting self-hatred at baseline has been found to predict higher levels of depression in adolescents after 12 months (McKenzie et al., 2011). Both these symptoms, *Loneliness* and *Self-hatred*, were also associated with a poor-quality mother relationship, the factor with the strongest impact on *Depression severity* and associated with the largest number of symptoms in the symptom networks. Therefore, targeting interventions at this node (*Relationship with mother*) also may have the ability to make a large impact through its associations with these two highly connected nodes, and may provide an easier, more tangible treatment target. In the study on depression and inflammation described in Chapter 6, *Loss of energy* had the highest centrality, based on combined Strength and Degree metrics, and highest predictability. Similarly, in a review of

central symptoms in network studies, Malgaroli et al. (2021) found that fatigue (aligned with, although not identical to, loss of energy) was overall the most central symptom (along with depressed mood) and suggested that clinical interventions should consider monitoring and targeting fatigue. In the study in Chapter 3, *Energy levels* were significantly associated with every depression symptom in bivariate analysis. Fatigue is one of the most prevalent presenting symptoms of major depression; it is consistently associated with impaired concentration, irritability, and reduced productivity (Targum & Fava, 2011). Adolescents get trapped within cycles of fatigue yet, this is often not seen as a priority amongst clinicians (Higson-Sweeney et al., 2024). Its prevalence in network studies as an influential symptom, may help draw more attention to fatigue as an important and potentially productive target in depression treatments.

7.3.3. Cultural Considerations and Implications

Measuring depression at the symptom item level, within a systems approach such as network analysis, facilitates nuanced findings that may identify culturally specific aspects of depression. Other studies have used network analysis to investigate cross-cultural robustness of findings (Mihić et al., 2024; Wasil et al., 2021), or viewed the network analysis results through a cultural lens, particularly in reference to central nodes (Kim et al., 2021; Osborn et al., 2020; Wasil et al., 2020), but few studies, if any, have used multiple network inferences to investigate the interactions between culture and symptom expression in depression.

In the studies investigating adolescent depression risk factors and suicidality (Chapters 3 and 4), the depression symptom related to *Negativity towards looks* was consistently predominant. In the study in Chapter 3, *Negativity towards looks* was weakly associated with *Depression severity*, but in the depression symptom network, the link between *Negativity towards looks* and *Self-assessed weight* was the most reliable edge in the network. *Negativity towards looks* was one of only two symptoms associated with both *Self-harm* and *Suicidality*, the other being *Sadness.* There was a very strong edge between the symptoms of *Negativity towards looks* and *Self-hatred* in the studies described in Chapters 3 and 4, which makes having a negative self-image a possible risk factor for worsening of depression (McKenzie et al., 2011). These facts make intervening on this symptom essential for this cohort. The prevalence of this symptom may be the result of the age of the cohort, as research has found that negative perceptions of looks and in particular body image is a major risk factor for depressive symptoms, suicidality, and self-harm amongst adolescents across cultures, in cross-sectional and longitudinal research (e.g. Blashill & Wilhelm, 2014; Kostanski & Gullone, 1998; Murray et al., 2018; Rierdan et al., 1989; Siegel, 2002). Although the association has been found to be stronger in adolescent females, it also affects adolescent males (Blashill & Wilhelm, 2014), and adolescents' self-esteem and self-worth are often under attack from the constant promotion of unrealistic body

ideals on social media (Gomez-Castillo et al., 2022; Marengo et al., 2018). Based on its impact on adolescent mental health, it could be beneficial to include in high school health and depression prevention curriculum plans, education around building self-esteem, body positivity, and being resilient to unhealthy social media influence. Interventions that build self-esteem have been linked to building body confidence (O'Dea & Abraham, 2000), and the results from this thesis endorse this as *Self-assessed weight* was directly linked to *Depression severity* and the depression symptom *Negativity towards looks*, but actual *BMI* was only linked to *Negativity towards* indirectly through this self-perception variable.

In terms of non-symptom risk factors for depression and suicidality, a quality relationship with one's mother or main guardian, presence of school connectedness and quality peer relationships came through as valuable protective factors for this cohort (or risk factors when the relationships were poor and there was an absence of school connectedness) for both depression and suicidality. A quality relationship with one's mother (or guardian) shared a very strong edge with a quality relationship with one's father, making both influential. The importance of these factors in providing safeguards against depression symptoms and suicidality, is reflective of the age of the cohort, but there is evidence that its importance within this study is also the result of the Pacific Island cultural values. Research has found indications that Pacific people hold more collectivist views than some other groups, such as NZ Europeans (Podsiadlowski & Fox, 2011), and this increases the need for healthy community connections for wellbeing. It also means that a breakdown in relationships with family, partners, and friends is likely to be felt more keenly. Aoelua (2018) found that amongst NZ Pacific adolescents presenting at hospital after a suicide attempt, family and relationship conflicts were major precipitants. Research has found that network structures can vary by race/ ethnicity, and cultural factors and values are thought to be major drivers of this (Kim et al., 2021; Osborn et al., 2020; Wasil et al., 2020). Based on the primary importance placed on quality parental and friend relationships, in particular the role of the mother or main guardian, the influence of this association could be used to help build body positivity, by also advising and educating parents on the importance of this, on how to help build body confidence in their children, and not to be critical of the child's appearance. Similarly, the value placed on friends and school connectedness amongst this cohort, and the strong association between the two, suggests that using schools more to promote mental wellbeing and having adequate and trained in-school resources to help tackle psychological issues of Pacific high school students, and high school students generally, would be a valuable approach. In the case of Pacific students, this is likely to require councillors with Pacific heritage who are also cognisant of Pacific values.

Pessimism was the depression symptom that contributed most to *Suicidality,* in the study described in Chapter 4. This was in line with the findings from another network study with

Chilean adolescents, which found a very strong link between pessimism and suicide ideation (Núñez et al., 2018) but contrasted with the findings from another study with Dutch adolescents, where loneliness, sadness, self-hatred, and self-blame all had stronger associations with suicide ideation compared to pessimism (Gijzen et al., 2021). High levels of pessimism could be seen as a warning sign of possible suicidality in Pacific adolescents, as pessimism has been found to predict actual suicide better than a sum score of depression symptoms (Beck et al., (1988). This could be vitally important in situations where adolescents may not feel able to be open about their feelings of suicidality or deteriorating mental health because of cultural taboos. This is very relevant for this cohort, as there is evidence that Pacific people are less likely to seek help for depression and other mental health conditions because of perceived stigma associated with mental health problems (Subica et al., 2019).

In the study described in Chapter 3, *Loneliness* was the most central node, followed by *Self-hatred*. Network researchers have posited that it could be the collectivist versus individualist culture that may be influencing centrality findings (Kim et al., 2021; Osborn et al., 2020; Wasil et al., 2020). Wasil et al. (2020) found that the symptom feeling like a failure was much more central in the network of Indian adolescents compared to another network study of US adolescents, where 'Self-hatred' was the most central symptom (Mullarkey et al., 2019). Wasil et al (2020) surmised that it may be the pressure of Indian adolescents to live up to their parents' expectations, and the collectivistic culture in Indian society. Kim et al. (2021), in a network study of Asian pre-adolescents, also found loneliness to be the most central symptom and surmised the high influence of loneliness in the network was due to the collectivistic culture in Asian countries that emphasizes harmonic interactions with relevant communities. As outlined above, research has found that Pacific culture is also collectivist, and this could account for the high centrality of *Loneliness* in the symptom networks, combining this cultural intelligence with network inferences gives a more contextual understanding of what may be driving the loneliness, that is poor quality connections with family, friends, and the school community.

In contrast to the findings from Chapters 3 and 4, which exhibited potentially culturally influenced findings, in the study described in Chapter 6, the results exhibited cross cultural robustness, when compared with other studies, which were very similar procedurally, but with very different cohorts, in terms of ethnicity, culture, and age profile. The reason is likely to lie in the nature of the non-symptom variables included in the networks. The variables included in the studies described in Chapters 3 and 4 were mostly from psychosocial domain. In Chapter 5, which was investigating associations between depression and inflammation, the non-symptom variables included biological markers of inflammation, alongside a limited range of health and lifestyle related variables (BMI, alcohol consumption, exercise, and smoking), and gender.

The study in Chapter 6 was a procedural replication of three other network studies, two conducted with US participants (Lee et al., 2023; Moriarity et al., 2021) and one with Dutch participants (Fried et al., 2020). In the study described in Chapter 6, all participants were aged 19 or 20, from NZ and with at least one parent who identified as Pacific. In the Dutch study, the majority of participants were White (Penninx et al., 2008), with a mean age of 41 years. In Moriarity et al. (2021), the participants were racially diverse, divided primarily between white, Mexican or other Hispanic, and Non-Hispanic Black, with a mean age of 47 years. In the study by Lee et al. (2023), all participants were from the US, but ethnicity was not stated, with a mean age of 73. All studies, including the one in this thesis described in Chapter 6, found associations between CRP and symptoms related to appetite disturbance (Fried et al., 2020; Gossage et al., 2024; Lee et al., 2023; Moriarity et al., 2021), but there were differences. In the three other network studies, appetite disturbance was measured as a compound symptom, where the nature of the disturbance (increased or decreased) was combined, and it was this compound symptom that was associated with CRP (Fried et al., 2020; Lee et al., 2023; Moriarity et al., 2021), but in Fried et al. (2020) the association disappeared after covariate adjustment. In the study in Chapter 6, *Appetite disturbance* was measured both as a compound symptom and disaggregated into increased and decreased, but only *Increased appetite* was associated with *CRP*. Other similar findings between the study in Chapter 6 and these other network studies, were related to associations between inflammatory markers with hypersomnia and fatigue / energy related symptoms. In Fried et al. (2020), hypersomnia was related to all inflammatory markers, including CRP. In Moriarity et al. (2021), decreased energy was associated with CRP (the only inflammatory marker studied). Other than associations between CRP with appetite disturbance, Lee et al. (2023) did not find any other associations between CRP (the only biomarker studied) and depression symptoms. In the study in Chapter 6, *CRP* was not directly associated with hypersomnia (*Increased sleep*) or fatigue / energy related symptoms but was indirectly associated with these symptoms through *Increased appetite*. Therefore, there was a high level of concordance between the findings of the study in Chapter 6 and these other network studies that were conducted with very different cohorts, ethnically and socio-demographically. In all studies, CRP was strongly associated with BMI, including the study in Chapter 6.

Based on these results, if the network approach is to achieve its capacity to provide detailed information that could aid clinical decision making, then networks with diverse ethnic and cultural populations are required, as the generalizability of results cannot be assumed. It is vital to take these factors into account when planning depression prevention and treatment strategies, as evidence shows that one size does not fit all, as was shown in the studies in Chapters 3 and 4 into depression risk factors and suicidality. However, when results are similar across different populations, this strengthens the generalizability of findings, as occurred here in the study in Chapter 6 investigating inflammation and depression

7.4. Theoretical Contribution: Implications for Depression Measurement

As well the findings from the studies in this thesis having clinical implications for depression and suicidality assessment and treatment, they also add empirical weight to calls urging for changes in the way the concept of depression is measured (Fried et al., 2022). Sum scores have been shown to be too blunt a tool with which to assess depression, which is arguably made up of diverse and multiple conditions, based on varying symptom profiles and clusters, as suggested elsewhere (Fried & Cramer, 2017). Yet despite clinicians and depression researchers raising concerns about sum scores decades ago (Ma & Teasdale, 2004), with calls for a psychometric re-evaluation in the way depression is diagnosed (Lux & Kendler, 2010), this is still the predominant way that depression is measured (Fried et al., 2022).

Fried et al. (2022) argue that these traditional methods of measuring depression, such as sum scores and discrete diagnosis categories based on cutoffs, are not in step with progress in relation to depression theories. The overall findings from this thesis concur with this view, that using only depression sum scores or even depression symptom dimensions do not provide enough granular detail to capture the complexities of depression and lead to a loss of valuable information. Using sum scores and categorical definitions may still be useful and practical to get an assessment of severity but should be used in conjunction with other measurement instruments, including depression measured in terms of smaller units, such as symptoms. Researchers are suggesting that the best approach may be multi-modal (Fried, 2015), and support for a multi-modal approach was found in this thesis. In the study described in Chapter 3, on risk factors for depression, gender and energy levels were associated with *Depression severity*, but not with any depression symptoms. There is evidence also that some symptoms signify greater depression severity than others, in particular symptoms related to suicidality and self-hatred. Suicide ideation has been found to be an indicator of more severe and chronic depression (Gijzen et al., 2021; Lux & Kendler, 2010), and in the study in Chapter 4, suicidality was associated higher symptom severity of every individual depression symptom. Therefore, where sum scores of symptoms are to be used, a psychometric re-evaluation of depression symptoms with a view to weighting those indicative of more severity could be warranted.

If there is to be more emphasis on individual depression symptoms to measure depression syndromes, then the lack of standardisation of depression instruments could prove problematic, as has been pointed out elsewhere (Fried, 2017; Fried et al., 2022). The study described in Chapter 6 showed how using compound symptoms can obfuscate findings and may even be holding up the identification of inflammatory biomarkers for depression. These findings suggest any overhaul of depression instruments should include disaggregating symptoms related to sleep and appetite as a standard. Aggregation, even at the symptom level has the potential to lead to

obfuscation, as the study in Chapter 6 showed. There were also problems comparing some of the findings of the study in Chapter 6 with the other studies it was procedurally replicating because of the lack of consistency of symptoms included in the various depression instruments. For example, in the study in Chapter 6, an association was found between *CRP* and *Loss of libido,* but this could not be compared with the findings from two of three studies it was procedurally replicating as they used depression inventories that did not include a symptom related to libido.

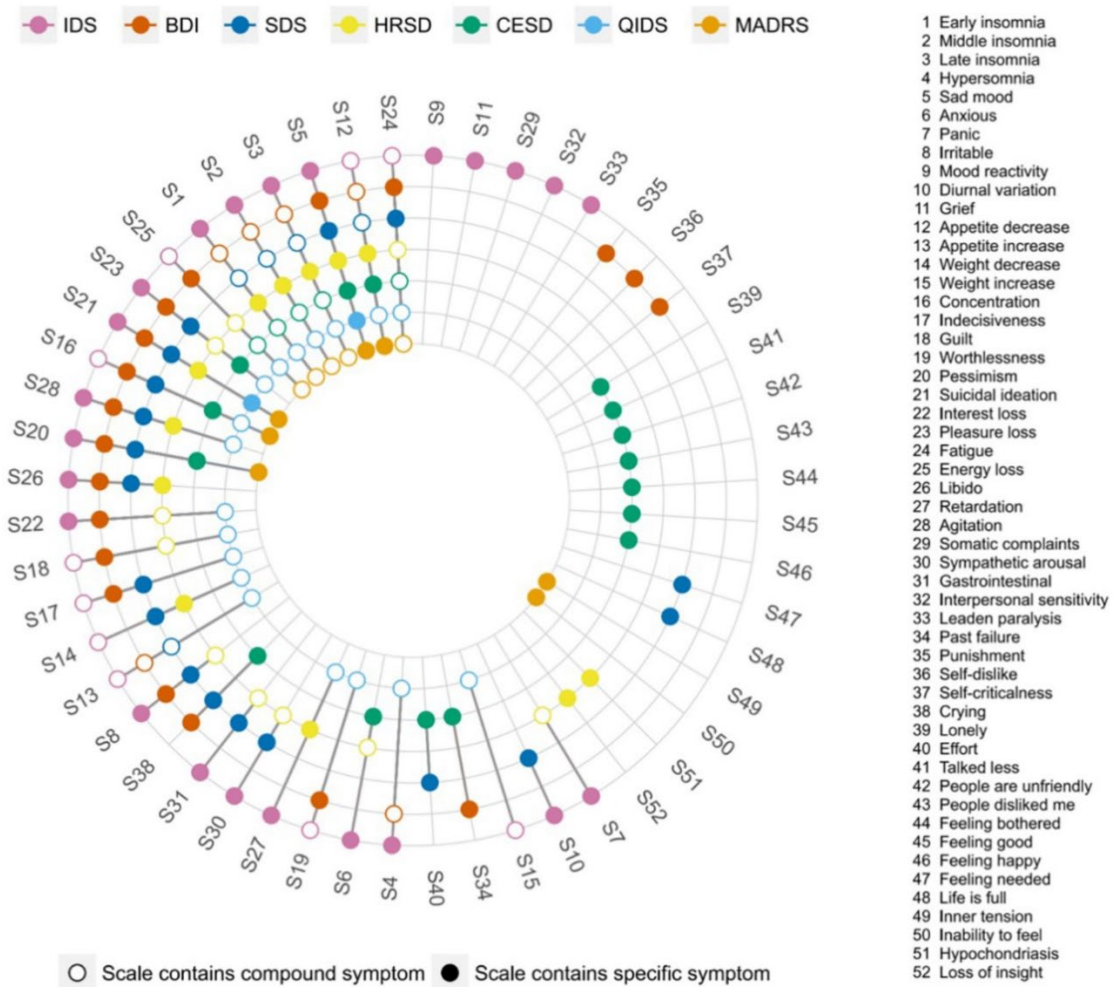

Figure 12 Co-occurrence of 52 symptoms across 7 depression rating scales

Reprinted with permission from *Journal of Affective Disorders, 208*, Fried, E. I., The 52 symptoms of major depression: Lack of content overlap among seven common depression scales, 191-197, Copyright (2017), with permission from Elsevier.

The diagram above is from a paper by Fried (2017), which aimed to draw attention to this issue of lack of standardisation in depression inventories. It highlights the inconsistencies between inventories in terms of which symptoms are included and in which form. It also shows which inventories represent symptoms related to appetite and sleep, for example, as compound symptoms and which disaggregate these symptoms into increased and decreased.

Another aspect of depression measurement needing attention is cultural considerations. Depression inventories were predominantly created by clinicians from the industrialized west for depressed subjects from the industrialized west (Fried et al., 2022). Any psychiatric re-evaluation needs to involve diverse groups, as symptoms and other risk factors may not represent the same constructs in different cultures. A good example of this is with the construct for self-harm. Dash et al. (2017) found that what constitutes self-harm differs by cultures, with understandings of self-harm including excess alcohol intake and damage to mental self as well as intentional harm to the physical self, amongst Pacific people within a NZ context. If items on inventories or risk factors are not measuring the same construct for all groups, then this would limit progress with certain groups and make comparing findings across ethnic and social groups difficult. It is also valuable to investigate how cultural factors could influence dynamic relationships between symptoms. In the study described in Chapter 2, lacking friendship was associated with school connectedness, which was in turn was associated with school attendance, indicating the importance of community to Pacific adolescents. Hinton et al. (2021) found that fear of certain anxiety symptoms and their physical manifestations amongst Cambodians comprised a cultural syndrome and suggested additions to the Anxiety Sensitivity Index to assess worry about anxiety symptoms that is salient in certain cultures.

Fried (2015) suggests a type of depression-measurement approach which involves focussing on symptoms or on small clusters of symptoms, identifiable through systems approaches, such as network analysis. According to the network approach, symptoms cluster because of causal interactions, but Fried (2015) also suggests that these symptom clusters may share an underlying mechanism (Fried, 2015). This conceptualization of depression could help link these symptom clusters with certain conditions, traits, or characteristics, such as inflammation or cultural considerations. Fried and Cramer (2017) argue that depression 'symptomics', that is the analysis of depression in terms of individual symptoms, symptom interactions, and symptom clusters, provides a better model for understanding depression and provides clinically relevant information. This way of conceptualizing depression paves the way for seeing depression in terms of multiple syndromes and expanding the current depression dimensions and subtypes that are regularly used as a basis for research. Going forward, when conducting clinical trials to test depression medications or other treatments, depressed groups could be included based on having similar symptom presentations, rather than using diagnostic measures of depressed / not depressed, for example, so that the depressed group is less heterogeneous in terms of symptom profiles. It is also recommended that clinical trials should monitor which symptoms improve or not in response to anti-depressants, rather than measure improvement in depression overall (Fried & Cramer, 2017). Other types of therapeutic intervention would also benefit from this approach, as symptoms vary in their response to treatment, and network analysis can be used to monitor symptom improvement (Mullarkey et al., 2020). Using small symptom clusters, rather

than depression measured as a sum score or as a dimension or subtype, may also be a way to progress the identification of depression biomarkers as, as shown in this thesis and other studies (e.g. Fried et al., 2020; Lamers et al., 2018; Lee et al., 2023; Milaneschi et al., 2021; Moriarity et al., 2021), certain symptoms are much more likely to be associated with inflammation than others. In recent years, the growing popularity of techniques such as network analysis, which emphasize a symptom-level approach to measure depression, may result in a shift to a 'new normal'. Such a paradigm shift in the way depression is measured is not likely to happen overnight, but to be brought about by a persuasive body of research, including research such as in this thesis, which illustrates how much more information is available by measuring depression in terms of smaller units, for example symptoms and symptom clusters, and the powerful detail this can provide for potential treatments.

7.5. Limitations

The conclusions drawn from this thesis should be considered in the light of a number of limitations.

7.5.1. Sample and Study Design

One of the main limitations was the cross-sectional design used in all original studies, meaning that causality could not be established. However, the network structures and conditional dependency relationships within the networks provide indications of causal relationships that can be tested with temporal data or experimental designs. The analyses did not include data from disorders or conditions other than depression, whose symptoms may overlap. Similarly, it is possible that an association identified within the network is really the result of another variable not included in the analyses. The community samples used were homogeneous as regards ethnicity, age, and socio-economic status, so the results may not generalise to other populations or clinical samples. Although inferences were made about some of the findings being culturally shaped, it is possible that this was driven by other factors, such as socio-economics. Pacific New Zealanders in the studies were treated as one composite ethnic group, because the samples were not large enough to divide them into separate Pacific ethnic groups. The results for separate ethnic groups may, however, differ in relation to findings of the studies. The Specific limitations relevant to the original studies (Chapters 3, 4, and 6) are detailed within the chapters describing those studies.

7.5.2. Depression Measurement

The construct that the individual depression symptoms measured was based on a single indicator, thus making it impossible to calculate measurement error for these items (de Ron et al., 2022), although depression was also measured as one or more latent variables to accompany the symptom level analyses in most studies. The depression data was self-reported and there

were issues with missing depression data for the PIF Study year-17 sample. It is also not known how appropriate the depression instruments used are for young Pacific New Zealanders, as they have not been specifically tested with this group.

7.5.3. Network Approach to Psychopathology

The network approach is still in its infancy or at best youth. This means that the underpinnings of network theory are largely untested. Insights from networks need to be tested using temporal data and randomised controlled experiments. It is not known, for example, with confidence whether intervening on a node with high centrality has more impact than a peripheral node, although studies are starting to move to this experimental testing level to validate the propositions inherent in the network approach, and methodologies are being developed to guide such intervention processes (see Borsboom, 2022 for an overview of work in this area).

7.6. Directions for Future Research

7.6.1. For the Studied Population

"Out of adversity comes opportunity" (Benjamin Franklin), and the directions for future research have largely emerged from the thesis limitations. The network structures that resulted from estimating the networks in the original studies provided indicators of possible causal relationships, which could be tested with temporal data or using experimental research design. This would provide deeper insight, for example, into the direction of the association between poor-quality mother relationship with depression symptoms and *Depression severity* (Chapter 3); how *Negativity towards looks* may be contributing to *Suicidality* (Chapter 4); the dynamics of the possible feedback loops or indirect associations identified, such as between *Impulsivity*, *Delinquency* and *Self-criticalness* (Chapter 6); and the temporal order of the relationship between the symptoms *Increased appetite* and *Loss of libido* with *CRP*, to test whether it is inflammation that could be disrupting appetite regulation and/ or libido or the other way around. Future research with larger sample sizes could also discover whether there are significant differences between the ethnic groups in relation to associations between depression symptoms with risk factors, suicidality, and inflammation, to further refine and target treatments and therapies. However, the thesis did produce many useful results in relation to depression and suicidality amongst Pacific New Zealanders. Going forward, working with practitioners within Pacific mental health programmes on ways to practically and sensitively apply or test some of these findings should be investigated.

7.6.2. For Depression Measurement

There are many advantages of measuring depression in terms of granular items such as individual symptoms, but as outlined above measuring symptoms in terms of a single indicator prevents quantifying measurement error. Therefore, researchers recommend multiple indicators

per item (Fried et al., 2022), which would enable measurement error to be calculated. The trade-off is high levels of accuracy versus low levels of participant burden, so future research should examine where this line could be drawn to satisfy both. New mobile technologies could be used to provide innovative ways to collect data relevant to depression symptom constructs, and information on interactions between symptoms with the environment setting in real time. This could lead to a wealth of temporal data that could be used to measure depression symptom constructs, and its potential is already being investigated (Hartmann et al., 2019; Sequeira et al., 2020). This study also uncovered two important areas for future research relevant to depression measurement. As stated in limitations, it is not known how suitable the most commonly used inventories are for diverse cultures, such as Pacific people, which have more collectivist values than in Europe and United States. Therefore, future work should test the psychometric properties of the most commonly used scales to test their suitability for other cultures that may have different value systems. Secondly, whether certain symptoms on depression inventories should be weighted could be explored. In some research situations it may be necessary or desirable to use latent constructs and they are a very useful method for variable reduction, but there are real measurement issues when all symptoms are treated as interchangeable as this treats suicide ideation equivalent to concentration problems, for example. So, rather than reject the latent variable approach completely, with its assumptions of symptom interchangeability, ways to improve it should be explored; for example, the use of factor scores rather than raw scores could be investigated.

7.6.3. For the Network Approach to Psychopathology

To help the network approach move to fulfil its objectives as an aid to clinical decision making more research is needed on testing effects of intervening on a node in experimental conditions. Amongst network pioneers this fact is well documented, and plans are underfoot to help fill this gap between empirical models and testable theories (Borsboom, 2022). Psychological networks also have a lot of potential to increase a patient's involvement in their treatment. The network graph is very intuitive and at a basic level can be interpreted by non-statisticians. By creating individualised networks with time series data, patients could monitor symptom associations and changes and become actively involved in their own treatment.

Methodologically, another area that could be addressed in the future is how best to combine variables from different domains within one network. Non-symptom variables from across various domains are increasingly being included in psychological network studies. Intra domain network connections are more likely than inter domain connections, particularly between biological and psychosocial data, for example. When regularization is used, inter domain connections that may be of interest could be shrunk to zero. In this thesis, this was addressed by fitting regularized and unregularized networks and then testing reliability of the connections

with bootstrapping, but there may be ways of stratifying networks so that the regularization or other variable selection methods can penalise complexity more harshly within levels compared to between levels.

7.7. Summary

The current thesis applied the network approach to psychopathology to obtain a deeper, more nuanced and granular understanding of the relationships between depression symptoms with risk factors, suicidality, and inflammation amongst NZ Pacific adolescents and young adults. It conducted three original studies and a literature review. The findings from the original studies presented in this thesis, or at least aspects of them, have the potential to be taken forward into clinical settings in some form and other forums involved in the prevention and treatment of depression and suicidality amongst young NZ Pacific people. The findings also have broader implications in the areas of depression measurement and the use of the network approach to psychopathology. They provide empirical support to the perspective that measuring depression only as a sum score of symptoms or in terms of a binary diagnosis, obscures valuable information that could be used to target treatments at depressed and suicidal people, and those suffering depression and inflammation, with more accuracy and effectiveness. Methods measuring depression need to capture the heterogeneity of depression symptom profiles, which could occur alongside latent variable approaches. The thesis also demonstrated how the network approach provides a contextual and intricate framework for analysing relationships at various levels of the network, and this additional insight has the potential to advance depression treatment and aid the identification of new depression subtypes, most likely based on small symptom clusters. The thesis also showed how the network approach can be leveraged to advance understanding of the impact of culture on the psychopathology of depression and suicidality with subsequent implications for treatment.

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Appendix A

Centrality plots for depression symptoms Chapter 3

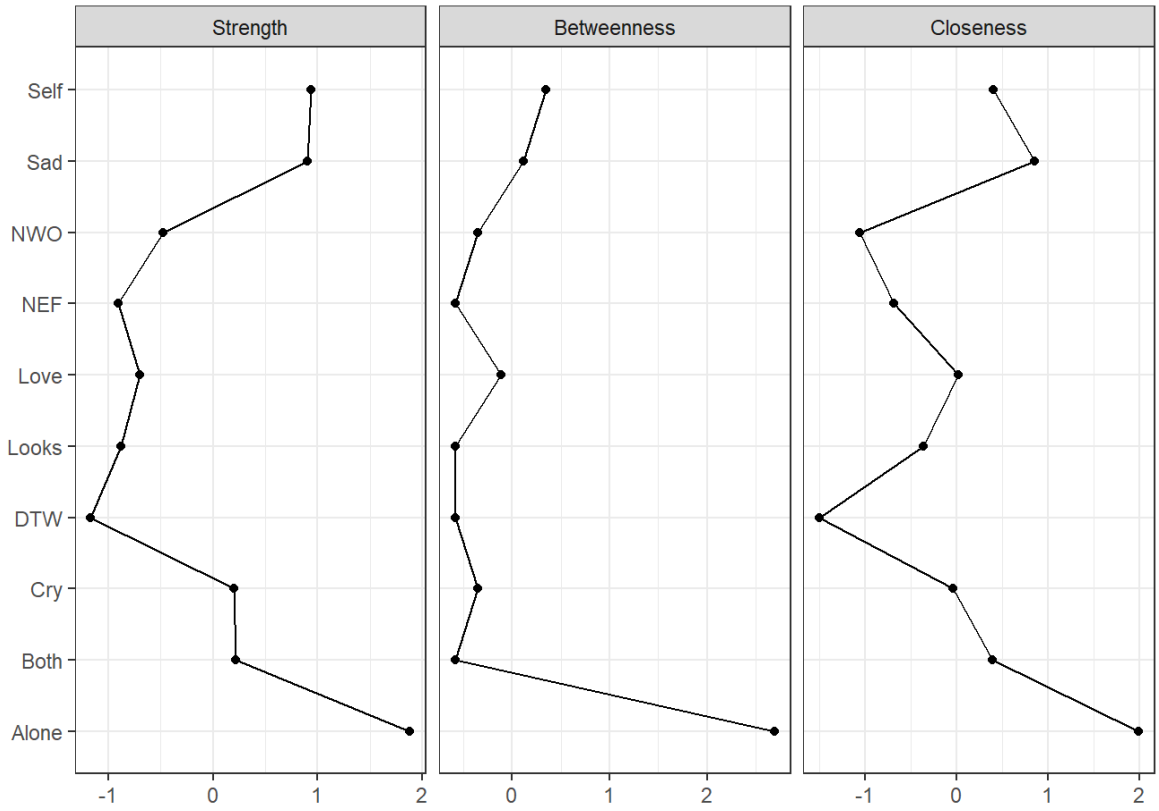


Figure A-1. Centrality indices of individual depression symptoms, shown as standardized z-score values in a sample of 561 Pacific New Zealand adolescents aged 16-17 years. Data from the Pacific Island Families Study. The x-axis shows the standardized z-score, the y-axis the node labels of the individual symptoms. Legend of node labels and depression symptoms: Alone (*alone*), Sad (*sad*), Cry (*cry*), Look (*looks*), Both (*bothered*), NEF (*not enough friends*), NWO (*not work out*), DTW (*does things wrong*), Self (*self-hatred*), Love (*love*). Alone is by far the most central symptom. It has the highest scores for all three centrality measures.

Descriptive Data Tables

The **Table A-1** shows supplementary descriptions and distributions of all analysis variables for the study in Chapter 3. **Table A-1** is too large to reproduce here and so is in the accompanying electronic folder Appendix A filename: **Table A-1 Descriptive data**

Table A-2 Psychometric inventories used to measure analysis variables in Chapter 3 and Chapter 4

Variables	Inventory	Items	Scoring
Relationship with mother, Relationship with father, Relationship with friends	Inventory of Parent and Peer Attachment - Revised (Armsden & Greenberg, 1987)	25 items for each inventory	Items score 1 to 5, 1=Never true, 5= Variables created by summing up items, after any necessary reverse scoring, to create a scale. Higher scale scores imply better relationship.
Impulsivity	Impulsivity scale (four items) (Bosworth & Espelage, 1995)	4 items	Items score 1 to 5, 1=Never, 5=Always. Variables created by summing up items, to create a scale. Higher scale scores imply more impulsiveness and less self control.
Delinquency	Modified version of the Disciplinary and Delinquent Behaviour scale (Dahlberg, Toal, Swahn, & Behrens, 2005)	8 items	Items score 1 to 5, 1=Never, 5=10 or more times. Variables created by summing up items, to create a scale. Higher scale scores imply more delinquent behaviour.
Gang involvement	Modified version of the Gang Membership Inventory (Pillen & Hoewing-Roberson, 1992)	3 items	Items scored 1 to 2, 1=No, 2=Yes. Variable created by summing items and then binarizing. A 'Yes' answer to any of the three items coded as 1, and 'No' to all three items coded as 0.
Resilience	Modified version of the Resilience scale (Chua, Milfont, & Jose, 2015), which was	4 items	Items scored 1 to 5, 1=Never, 5=Always

Weighted Adjacency Matrices for Chapter 3

The tables (A-3 to A-8) listed here show the weighted adjacency matrices relevant to the analyses in Chapter 3. They stored electronically in folder Appendix A as they are too large to reproduce here. The details of each table and associated filename are given below.

Table A-3 shows the weighted adjacency matrix for the relationships shown in the Figure 3 Network showing the relationships between Depression severity and the explanatory variables, gamma = 0.25, n=561. Table A-1is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-3 wadj dep sev 0.25**

Table A-4 shows the weighted adjacency matrix for the relationships between Depression severity and the explanatory variables, gamma = 0.5, n=561. It includes the same variables as Table A-3, but the pairwise interactions have been estimated with a higher value for gamma. Table A-4 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-4 wadj dep sev 0.5**

Table A-5 shows the weighted adjacency matrix for the relationships shown in the Network showing the relationships between individual depression symptoms and the explanatory variables, gamma = 0.25, n=561. Table A-5 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-5 wadj dep sym 0.25**

Table A-6 shows the weighted adjacency matrix for the relationships between individual depression symptoms and the explanatory variables, gamma = 0.5, n=561. It includes the same variables as Table A-5, but the pairwise interactions have been estimated with a higher value for gamma. Table A-6 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-6 wadj dep sym 0.5**

Table A-7 shows the weighted adjacency matrix for the relationships between *Depression severity* and all analysis variables, including the variables removed by applying the redundant node function in goldbricker (*PCB* and *Binge drinking*), gamma = 0.25, n=561. Table A-7 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-7 wadj dep sev all variables incl 0.25**

Table A-8 shows the weighted adjacency matrix for the relationships between individual depression symptoms and all analysis variables, including the variables removed by applying the redundant node function in goldbricker (*PCB* and *Binge drinking*), gamma = 0.25, n=561. Table A-8 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-8 wadj dep sym all variables incl 0.25**

Zero order correlation matrices for the variables in Chapter 3

The tables listed here (A-9 to A-12) show the zero-order correlation matrices relevant to the analyses in Chapter 3. They stored electronically in folder Appendix A as they are too large to reproduce here. The details of each table and associated filename are given below.

Table A-9 shows the zero order Spearman's correlations between the analyses variables in Chapter 3, with depression measured as Depression severity. Table A-9 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-9 cor mat dep sev**

Table A-10 shows the P values based on the zero order Spearman's correlations in Table A-9 for the analyses variables in Chapter 3, with depression measured as Depression severity. Table A-10 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-9 cor mat dep sev p vals**

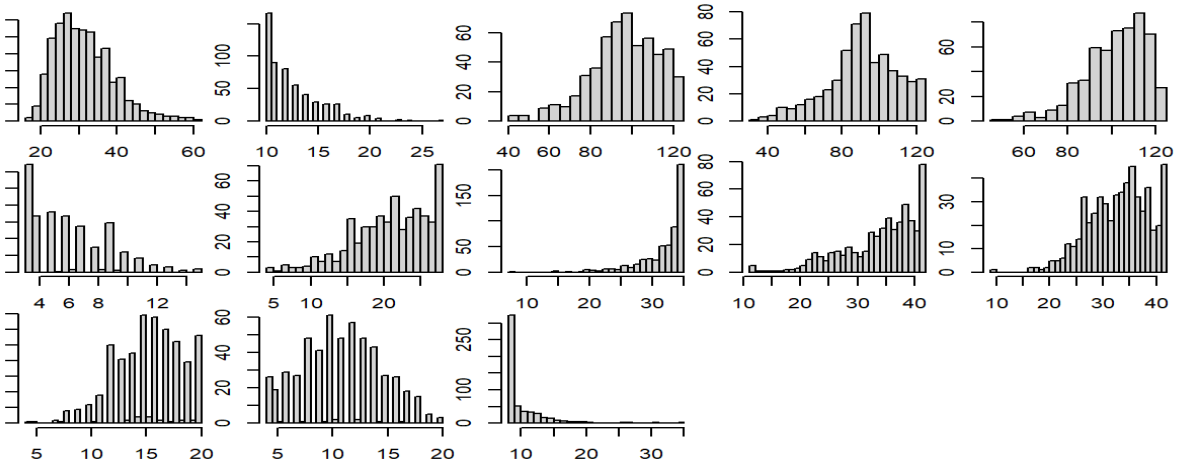
Table A-11 shows the zero order Spearman's correlations between the analyses variables in Chapter 3, with depression measured in terms of individual symptoms. Table A-11 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: Table A-11 cor mat dep sym

Table A-12 shows the P values based on the zero order Spearman's correlations in Table A-11 for the analyses variables in Chapter 3, with depression measured in terms of individual symptoms. Table A-12 is too large to reproduce here and so is in the accompanying electronic folder Appendix A, filename: **Table A-12 cor mat dep sym p vals**

Appendix B

Figure B-1

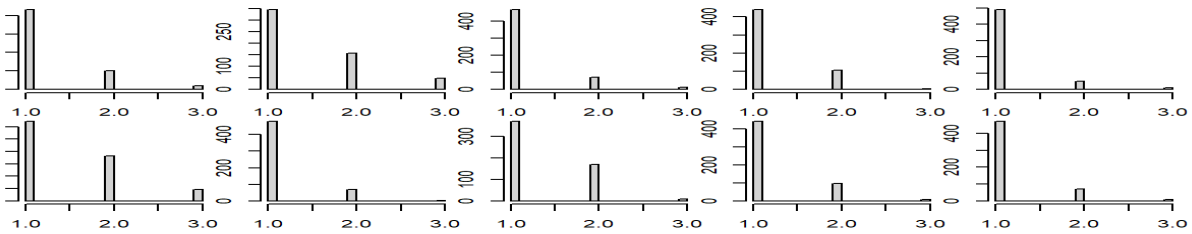
Histograms of continuous numeric variables in Chapter 4



Variables shown above in order:

Relationship with mother, Relationship with father, Relationship with friends, Negative peer influence, Cultural Efficacy (*CE*), Group Membership Evaluation (*GME*), Religious Centrality and Embeddedness (*RCE*), Pacific Connectedness and Belonging (*PCB*), *Resilience, Impulsivity*, and *Delinquency*.

Histograms of depression symptoms



Depression symptoms shown above in order:

Loneliness, Irritability, Crying, Self-criticism, Lack of friendship, Negativity towards looks, Feeling unloved, Pessimism, Sadness, and *Self-hatred*.

Table B-1 shows the distribution of analysis variables in Chapter 4 pre and post data imputation. Table B-1 is too large to reproduce here and so is in the accompanying electronic folder Appendix B, filename: **Table B-1 distribution pre and post imputation**

Table B-2 Results of the confirmatory factor analysis

Fit measures / Inventories	CFI	TLI	SRMR	RMSEA	df
Relationship with mother	0.92	0.92	0.08	0.08	275
Relationship with father	0.93	0.92	0.08	0.09	275
Relationship with friends[a]	0.91	0.90	0.08	0.10[a]	275
Impulsivity	0.99	0.98	0.02	0.06	2
Delinquency	0.98	0.97	0.05	0.05	20
Pacific Identity as sub scales (*CE, GME*, *PCB*, and *RCE*)	0.95	0.94	0.07	0.07	183
	Cronbach's alpha				
Resilience[b]	0.72				
Gang Involvement[b]	0.66				
Negative peer influence[b]	0.78				

[a]*Relationship wth friends* was at the upper end of the range for RMSEA in terms of acceptable model fit (0.1), but as all the other chosen CFA measures (CFI, TLI, SRMR, RMSEA) were within acceptable range it was fitted as one scale.

[b]The CFA models for *Resilience, Gang involvement*, and *Negative peer influence* were over saturated (df=0) as the inventories consisted of only three items. Therefore, Cronbach's alpha was used instead.

Table B-3 shows the bivariate associations between the analysis with the suicidality variable. Table B-3 is too large to reproduce here and so is in the accompanying electronic folder Appendix B, filename: **Table B-3 Bivariate analysis**

Predictability Statistics for the networks in Chapter 4

Table B-4 Predictability Statistics for Network A in Chapter 4

Variable	R2	Predictability of whole model	Predictability of intercept model	Additional predictability attributable to neighbouring nodes
Loneliness	0.386	NA	NA	
Irritability	0.277	NA	NA	
Crying	0.31	NA	NA	
Self-criticism	0.16	NA	NA	
Lack friendship	0.182	NA	NA	
Negativity towards looks	0.207	NA	NA	
Feeling unloved	0.187	NA	NA	
Pessimism	0.207	NA	NA	
Sadness	0.355	NA	NA	
Self-hatred	0.315	NA	NA	
Suicidality	NA	0.847	0.829	0.018

Table B-5 Predictability Statistics for Network B in Chapter 4

Variable	R2	Predictability of whole model	Predictability of intercept model	Additional predictability attributable to neighbouring nodes
Loneliness	0.388	NA	NA	
Irritability	0.279	NA	NA	
Crying	0.31	NA	NA	
Self-criticism	0.163	NA	NA	
Lack friendship	0.19	NA	NA	
Negativity towards looks	0.214	NA	NA	
Feeling unloved	0.186	NA	NA	
Pessimism	0.208	NA	NA	
Sadness	0.362	NA	NA	
Self-hatred	0.32	NA	NA	
Self-harm	NA	0.791	0.787	0.004
Suicidality	NA	0.864	0.83	0.034

The tables listed below (B-6 to B-7) show the predictability Statistics for Networks C and D in Chapter 4. They stored electronically in folder Appendix B as they are too large to reproduce here. The details of each table and associated filename are given below.

Table B-6 Predictability statistics for Network C in Chapter 4, folder Appendix B, filename: **Table B-6 Predictability Network C**

Table B-7 Predictability statistics for Network D in Chapter 4, folder Appendix B, filename: **Table B-7 Predictability Network D**

Weighted adjacency matrices for networks in Chapter 4

The tables listed here (B-8 to B-11) show the adjacency matrices for the networks in Chapter 4. They stored electronically in folder Appendix B as they are too large to reproduce here. The details of each table and associated filename are given below.

Table B-8 shows the weighted adjacency matrix for Network A, the relationships between individual depression symptoms and *Suicidality*, with regularization estimated with CV, n=550, folder Appendix B, filename: **Table B-5 Network A weighted adjacency matrix**

Table B-9 shows the weighted adjacency matrix for Network B, the relationships between individual depression symptoms with *Self-harm* and *Suicidality*, with regularization estimated with CV, n=550, folder Appendix B, filename: **Table B-9 Network A weighted adjacency matrix**

Table B-10 shows the weighted adjacency matrix for Network C, the relationships between individual depression symptoms, *Self-harm*, *Suicidality*, and all other non-symptom variables (except for the variables identified with goldbricker redundant node function and removed from the analysis (*PCB* and *Relationship with father*) with regularization estimated with CV, n=550, folder Appendix B, filename: **Table B-10 Network A weighted adjacency matrix**

Table B-11 shows the weighted adjacency matrix for Network D, the relationships between individual depression symptoms with *Self-harm, Suicidality*, and all other non-symptom variables, with regularization estimated with CV, n=550, folder Appendix B, filename: **Table B-10 Network A weighted adjacency matrix**

Appendix C

Table C-1 Inflammatory biomarker and depression statistics

Variable	N = 239
Inflammatory biomarkers	
CRP	
Mean (SD)	2.02 (2.16)
Median (IQR)	1.14 (0.41, 2.82)
IL-6	
Mean (SD)	26.81 (52.27)
Median (IQR)	10.40 (5.95, 19.40)
TNF-a	
Mean (SD)	10.11 (4.35)
Median (IQR)	9.30 (7.10, 12.40)
Depression measures	
Psychological depression	
Mean (SD)	3.79 (3.69)
Median (IQR)	3.00 (1.00, 6.00)
Sadness	
0	175 (73%)
1	64 (27%)
Pessimism	
0	165 (69%)
1	74 (31%)
Past failure	
0	133 (56%)
1	106 (44%)
Loss of pleasure	
0	150 (63%)
1	89 (37%)
Self-dislike	
0	169 (71%)
1	70 (29%)
Self-criticalness	
0	144 (60%)
1	95 (40%)
Suicidal thoughts	
0	206 (86%)
1	33 (14%)
Somatic depression	
Mean (SD)	4.62 (3.86)
Median (IQR)	4.00 (1.00, 7.00)
Loss of energy	
0	123 (51%)
1	116 (49%)
Sleep disturbance	
0	90 (38%)
1	149 (62%)

Increased sleep	
0	176 (74%)
1	63 (26%)
Decreased sleep	
0	153 (64%)
1	86 (36%)
Sleep disturbance (none/decreased/ increased)	
1	90 (38%)
2	86 (36%)
3	63 (26%)
Irritability	
0	176 (74%)
1	63 (26%)
Appetite disturbance	
0	111 (46%)
1	128 (54%)
Increased appetite	
0	180 (75%)
1	59 (25%)
Decreased appetite	
0	170 (71%)
1	69 (29%)
Appetite disturbance (none/increased/decreased)	
1	111 (46%)
2	69 (29%)
3	59 (25%)
Concentration difficulties	
0	154 (64%)
1	85 (36%)
Fatigue	
0	139 (58%)
1	100 (42%)
Loss of libido	
0	197 (82%)
1	42 (18%)

1 n (%)

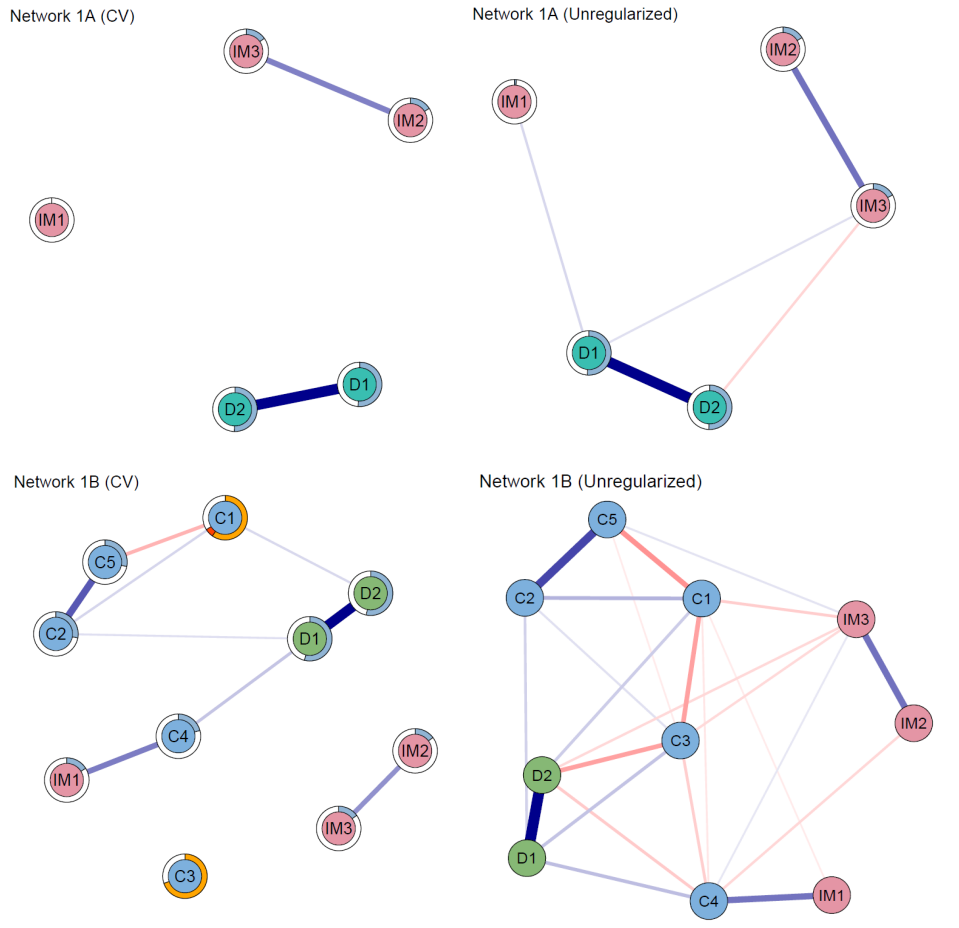


Fig C-1 Networks 1A (CV), 1A (Unreg), 1B (CV), and 1B (Unreg)
Legend: D1= Psychological depression, D2= Somatic depression, IM1= CRP, IM2= IL-6, IM3= TNF-a, C1= Gender, C2= Smoking, C3= Exercise, C4= BMI, C5= Alcohol

C-1 Supplementary information

Comparing sample characteristics

Mean BMI for the study sample was 33.5kg (SD=7.6kg), which was above the average for New Zealanders overall (28.6 kg) and in the obese range based on WHO guidance (World Health Organisation, 2024). However, it was only just over an ethnic-specific cutoff for overweight classification for Pacific people, based on previous research, which ranges from 26-32kg (Sundborn et al., 2010). It was much higher than the BMI in Fried et al. (2020), which was 25 kg/m^2, and somewhat higher than in Lee et al. (2023), which was 30 kg/m^2 (details of BMI were not stated in the Moriarity et al. (2021) study). The rate of present smokers (33%) was much higher than the national average in NZ of around 8% (SmokeFree, 2023), but the definitions of what constitutes a smoker may differ and the one used in the current study also included those who smoke very little and infrequently. Its rate was lower than current smokers in Fried et al. (2020), which was 38%, and recent smokers in Lee et al. (2023), which was 51%. Mean levels of CRP were within the normal range (mean =2.0 mg/L (SD=2.2)), and lower than in Lee et al. (2023), which was (4 mg /L), but the sample for that Lee et al. (2023) was much older which means a higher CRP on average. For IL-6 (mean=26.8 (SD=52.3)), and TNF-a (pg/mL) (mean =10.1 (SD=4.3)) levels were above those recommended for a healthy population. However, the medians were within healthy range (median IL-6=10.4 (IQR=13.45), and median TNF-a = 9.3 (IQR=5.3), indicating that some very high levels of these markers were skewing results. Further comparisons of sample statistics were not possible for all three studies this study was replicating as not all the details were published or different measurements were used to assess the covariates and so comparisons were not meaningful.

Additional parameter and statistical information relevant to the networks in Chapter 6

Bootstrapped Resamples for Chapter 6

The results of all bootstrapped resampling for Chapter 6 are in folder **Appendix C**, in subfolder **C-Bootstrapped samples**. Due to the large number of tables, the contents of this subfolder are listed in **Table C-2** below with descriptions.

Table C-2 Description of bootstrapped tables in Appendix C, C-Bootstrapped samples

Network	Estimation method	Filename
1A	EBIC	bs 1a ebic
1A	CV	bs 1a cv
1A	Unregularized	bs 1a unreg
1B	EBIC	bs 1b ebic
1B	CV	bs 1b cv
1B	Unregularized	bs 1b unreg
2CC	EBIC	bs 2cc ebic
2CC	CV	bs 2cc cv
2CC	Unregularized	bs 2cc unreg
2DC	EBIC	bs 2dc ebic
2DC	CV	bs 2dc cv
2DC	Unregularized	bs 2dc unreg
2CM	EBIC	bs 2cm ebic
2CM	CV	bs 2cm cv
2CM	Unregularized	bs 2cm unreg
2DM	EBIC	bs 2dm ebic
2DM	CV	bs 2dm cv
2DM	Unregularized	bs 2dm unreg
2CL	EBIC	bs 2cl ebic
2CL	CV	bs 2cl cv
2CL	Unregularized	bs 2cl unreg

2DL	EBIC	bs 2dl ebic
2DL	CV	bs 2dl cv
2DL	Unregularized	bs 2dl unreg
2CLM	EBIC	bs 2clm ebic
2CLM	CV	bs 2clm cv
2CLM	Unregularized	bs 2clm unreg
2DLM	EBIC	bs 2dlm ebic
2DLM	CV	bs 2dlm cv
2DLM	Unregularized	bs 2dlm unreg

Notes on the tables in folder Appendix C, subfolder C-Bootstrapped samples

For more detail on what distinguishes each network see Table 12 in Chapter 6.

The names of the variables within the tables are the same as the node labels in the networks, for convenience a legend is provided below.

The column 'Sample' is equivalent to the edge weight of the pairwise association.

The columns 'q2.5' and q97.5 show the 95% bootstrapped quantiles.

The column prop0 states the proportion out of 1 that the pairwise edge was set to zero in the 500 bootstrapped samples.

The column propnon0 states the proportion out of 1 that the pairwise edge was not zero in the 500 bootstrapped samples.

Legend of node labels

D1= Sadness, D2= Pessimism, D3= Past failure, D4= Loss of pleasure, D5= Self-dislike, D6= Self-criticalness, D7= Suicidal thoughts, DS1= Loss of energy, DS2= Sleep disturbance (presence / absence) DS2M = Increased sleep, DS2L= Decreased sleep, DS2LM= Sleep disturbance 3-level (none/ less/ more), DS3= Irritability, DS4= Appetite disturbance (presence / absence), DS4M= Increased appetite, DS4L= Decreased appetite, DS4LM= Appetite disturbance 3-level (none/ less/more), DS5= Concentration difficulties, DS6= Fatigue, DS7= Loss of libido, IM1= CRP, IM2=I L-6, IM3=

Table C-3 collates the predictability statistics and the centrality metrics for strength and Degree and shows the correlation stability coefficients

Network	2CC EBIC	2CC CV	2CC unreg
	Highest	DS1	DS1
Predictability	DS1	DS1	DS5
Strength	DS3	DS4, DS3, DS1, D6, D1, EQUAL	DS3
Degree	DS1, D6 EQUAL	Str 0.59	Str 0.36
Corstability	Str 0.51	Deg 0.44	Deg 0.28
Corstability	Deg 0.36		
Network	2DC EBIC	2DC CV	2DC Unreg
Predictability	DS1	DS1	DS1
Strength	DS1	DS1	DS4
Degree	DS1, DS2	DS1	N/A
Corstability	Str 0.52	Str 0.67	Str 0.29
	Deg 0.59	Deg 0.44	Deg 0.21

Network	2CM EBIC	2CM CV	2CM Unreg
Predictability	DS1	DS1	DS1
Strength	DS6	D2	D2
Degree	DS6, DS5, DS3, DS1 EQUAL	n/a	n/a
Corstability	Str 0.51	Str 0.52	Str 0.44
	Deg 0.36	Deg 0	Deg 0.13
Network	2DM EBIC	2DM CV	2DM Unreg
Predictability	DS1	DS1	DS1
Strength	DS6	DS1	DS4M
Degree	DS6, D4, DS3 EQUAL	n/a	n/a
Corstability	Str 0.51	Str 0.67	Str 0.36
	Deg 0.51	Deg 0	Deg 0.13
Network	2CL EBIC	2CL CV	2CL Unreg
Predictability	DS1	DS1	DS1
Strength	DS3	DS3	DS4L
Degree	DS3, DS5	DS3	n/a
Corstability	Str 0.51	Str 0.59	Str 0.44
	Deg 0.44	Deg 0.59	Deg 0.21

Network	2DL EBIC	2DL CV	2DL Unreg
Predictability	DS1	DS1	DS1
Strength	DS1	DS3	D2
Degree	DS1	D5	n/a
Corstability	Str 0.44	Str 0.59	Str 0.36
	Deg 0.52	Deg 0.36	Deg 0.13

Network	2CLM EBIC	2CLM CV	2CLM Unreg
Predictability	DS2LM	DS2LM	DS2LM
Strength	DS3	DS3	D2
Degree	DS1, DS3	n/a	n/a
Corstability	Str 0.44	Str 0.51	Str 0.36
	Deg 0.44	Deg 0	Deg 0.21

Network	2DLM EBIC	2DLM CV	2DLM Unreg
Predictability	DS1	DS2LM	DS2LM
Strength	DS1	D2, DS3	DS4LM
Degree	DS1, DS3 EQUAL	DS3, DS4LM	n/a
Corstability	Str 0.51	Str 0.59	Str 0.36
	Deg 0.59	Deg 0.36	Deg 0.21

Notes on Table C-3

The legend for the node labels is on page 191

Where it shows N/A on the table, this is because the correlation stability coefficient for Degree centrality did not meet the minimum threshold of 0.25, which means the results are not interpretable.