The role of inflammatory markers in explaining the association between depression and cardiovascular hospitalisations

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Conflict of interest

Sarah Hiles, Amanda Baker, Theo de Malmanche, Mark McEvoy, Michael Boyle and John Attia declare that they have no conflict of interest.

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all participants for being included in the study.

Abstract

This study investigated whether inflammation may explain the relationship between depression and incident cardiovascular hospitalisations. Participants (55-85 years) completed baseline depression and physical assessment. Those without self-reported cardiovascular events were followed prospectively for hospital admissions for angina, myocardial infarction and cerebral infarction (median 937 days). Across 5140 person-years of risk (*N* = 1692), there were 47 incident cardiovascular hospitalisations (2.8%). Controlling for age and gender, interleukin (IL)-6, C-reactive protein (CRP), body mass index (BMI) and waist-to-hip ratio were associated with future cardiovascular events. Mediation analysis showed that CRP accounted for 8.1% and IL-6 10.9% of the effect of depression on cardiovascular events, and including the indirect effect in the model substantially reduced the direct relationship between depression and cardiovascular hospitalisations. BMI and waist-to-hip ratio accounted for indirect effects of 7.7% and 10.4%, respectively. Inflammatory markers partly explain the association between depression and cardiovascular events, although other shared factors also likely contribute.

Keywords: Depression; inflammation; myocardial infarction; cerebral infarction; angina pectoris.

Introduction

Both depression and cardiovascular disease are common and associated with substantial disease burden globally (World Health Organization, 2008). They also commonly co-occur, where people with depression are at higher risk of developing cardiovascular disease and *vice versa* (Aben et al., 2003; Gallagher et al., 2012; Surtees, Wainwright, Luben, et al., 2008; Thombs et al., 2006; Van der Kooy et al., 2007). Individuals with both disorders concurrently have a substantially greater disease burden than either alone, with high rates of disability and complications (González & Tarraf, 2013; Rudisch & Nemeroff, 2003).

Although there is much evidence that depression poses a risk for the development of cardiovascular diseases and events, the mechanism of this relationship remains unclear. Inflammation may be involved since is closely related to both depression and cardiovascular disease. Firstly, pro-inflammatory markers are elevated in people with depression and may predict the development of depressive disorders (Dowlati et al., 2010; Hiles, Baker, de Malmanche, & Attia, 2012b; Howren, Lamkin, & Suls, 2009; Matthews et al., 2010; Pasco, Nicholson, et al., 2010). Prolonged elevations of inflammatory mediators are associated with changes to many of the hallmark biological features of depression, including neuroendocrine stress activity, neurotransmitter activity, neurodegeneration and oxidative stress (Miller, Maletic, & Raison, 2009). Secondly, pro-inflammatory markers are elevated in people with cardiovascular disease (Pearson et al., 2003) and predict risk of future cardiovascular disease (Danesh et al., 2008). Inflammation is implicated in the cause of atherosclerosis, involved in the formation and destabilisation of plaques (Hansson, 2005; Libby, Ridker, & Maseri, 2002). Furthermore, acute immune challenge transiently diminishes mood and modulates risk factors for cardiovascular disease including increasing diastolic blood pressure and changing heart rate variability via changes to the central autonomic system (Harrison, Cooper, Voon, Miles, & Critchley, 2013).

Many of the indicators of unhealthy behaviour that are observed in people with depression and cardiovascular events also contribute to chronic inflammation, including increased body mass index (BMI) or high waist-to-hip ratio, reduced physical activity, excessive alcohol intake, smoking and poor diet quality (Bonnet et al., 2005; Hamer, Molloy, de Oliveira, & Demakakos, 2009; O'Connor et al., 2009). In particular, adipose tissue stimulates the release of inflammatory mediators (Miller, Freedland, Carney, Stetler, & Banks, 2003; Shelton & Miller, 2010).

C-reactive protein (CRP), a broad marker of inflammation, has been identified as a predictor of both depression and cardiovascular disease, including stroke (Hemingway et al., 2010; Kuo et al., 2005; Matthews, et al., 2010; Ridker, Rifai, Rose, Buring, & Cook, 2002). CRP is released by the liver and promotes a pro-inflammatory response (Black, Kushner, & Samols, 2004). Levels of CRP spike during acute inflammation and low-grade elevations are observed in several chronic diseases, including cardiovascular disease and depression (Black, et al., 2004). Chronic elevation of CRP has been suggested as a diagnostic predictor of cardiovascular risk, independent of previously identified factors such as high low-density lipoprotein cholesterol and high blood pressure (Ridker, 2007), although this remains controversial (Hemingway, et al., 2010). Another pro-inflammatory marker particularly reliably associated with depression is interleukin (IL)-6 (Dowlati, et al., 2010; Hiles, et al., 2012b). The prospective studies and meta-analysis of Danesh et al. (2008) highlight that, like CRP, IL-6 is also associated with the development of coronary heart disease. CRP and IL-6 are relatively easily and inexpensively measured compared with other inflammatory markers, and make a good assessment of broad inflammatory status.

Separate studies have identified CRP (Ridker, 2007), IL-6 (Danesh, et al., 2008), and depressive symptoms (Van der Kooy, et al., 2007) as prospective predictors of cardiovascular events, although few have examined depression and inflammatory markers simultaneously and

prospectively in general community samples. Doing so allows the investigation of whether inflammation accounts for the observed relationship between depression and cardiovascular disease. The previous studies in community samples free of existing cardiovascular disease and/or events generally conclude that inflammatory markers and depression independently predict cardiovascular events, including coronary events (Davidson et al., 2009; Empana et al., 2005), cerebrovascular events (Arbelaez, Ariyo, Crum, Fried, & Ford, 2007) and mixed cardiovascular outcomes (Hamer, Molloy, & Stamatakis, 2008; Surtees, Wainwright, Boekholdt, et al., 2008). However, some studies indicate there is a synergy between inflammation and depression, for instance observing that CRP is only a key predictor of cardiovascular events in participants with depressive symptoms compared to those without (Ladwig, Marten-Mittag, Lowel, Doring, & Koenig, 2005), or observing the strongest association between depression and coronary heart disease for participants in the lowest quartile of CRP (Surtees, Wainwright, Boekholdt, et al., 2008). Studies conducted in samples with existing cardiovascular disease draw similar conclusions of an independent relationship between inflammatory markers, depression and cardiovascular events (Frazier, Vaughn, Willerson, Ballantyne, & Boerwinkle, 2009; Rallidis et al., 2011; Vaccarino et al., 2007; Whooley et al., 2008). However, one study indicated that participants with both low depressive symptoms and low CRP had low risk of further events, whereas participants with either high CRP or depressive symptoms were at similarly increased risk of events (Frasure-Smith et al., 2007). In these previous studies, the conclusion of independence is based on the observation that effect size only changes a small amount after adjusting for inflammatory markers in the association between depression and a future cardiovascular event. Previous studies have not estimated the size and significance of the indirect effect of depression on cardiovascular disease through inflammatory markers using a mediation framework.

The current study investigates whether the observed reliable association between inflammation and depression explains the relationship between depression and cardiovascular hospitalisations. Specifically, the aim was to investigate how much of the effect of depression on incident cardiovascular hospitalisation is accounted for by inflammation, as measured by the inflammatory markers CRP or IL-6. We then compared these effects to those obtained with BMI or waist-to-hip ratio as a mediator of the relationship.

Method

Participants

Participants were drawn from the Hunter Community Study – a study of the health of older persons in the regional city of Newcastle, Australia (for details see McEvoy et al., 2010). Briefly, between December 2004 and December 2007, community-dwelling individuals aged 55-85 years from the Newcastle area were randomly selected, stratified by age, from the Australian electoral roll and invited to participate in the study. 3318 individuals agreed (45%). The age, gender and marital status of participants enrolled in the Hunter Community Study were largely representative of regional, state and national profiles.

Procedures

Participants completed baseline self-report questionnaires and a face-to-face clinical assessment regarding health status, functioning, and health behaviours (see McEvoy, et al., 2010 for details on measures). Following baseline assessments, 2555 (78%) participants provided a serum blood sample for routine blood testing and for storage for future use. 2762 participants (83%) also consented to provide linkage with state hospital admissions records via the Centre for Health Record Linkage, which provided prospective surveillance data to the end of 2009 (median follow-up time 937 days).

Measures

Inflammatory markers: 12 hour fasting blood samples were collected, 95% in the morning. Samples were centrifuged at 4°C and 3000g for 10 minutes, and serum was stored at -80°C until analysis. High sensitivity CRP was analysed via CRP Flex System on Dimension Vista System immunonephelometry (Siemens Healthcare Diagnostics, Newark, DE, USA). The limit of detection was 0.16mg/L and coefficient of variation was 4.8%. High sensitivity IL-6 was analysed via Access IL-6 magnetic bead/chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA, USA, ref A16369), performed on a Beckman DxI. The lower limit of detection was 0.5pg/mL and coefficient of variation was 12%.

Depressive symptoms: Depressive symptoms were measured at baseline via the 20-item self-report Centre for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). It produces a continuous score (range 0-60) based on the frequency of depressive symptoms in the past week. The scale was designed for use in epidemiological studies and has been validated for use in older samples (Beekman et al., 1997). A cut-off score of 16 is used as a marker of at least mild and clinically relevant depressive symptomatology, and possible depression (100% sensitivity and 88% specificity for major depression) (Beekman, et al., 1997). Values were imputed if they were missing five or fewer items, based on the average of the items completed.

Cardiovascular hospitalisations: Hospital admission records were searched between 1st January 2004 and 31st December 2009 for separations where a relevant cardiovascular ICD-10 diagnosis appeared in the first three diagnosis coding positions. Relevant diagnoses included angina (I20), acute myocardial infarction (I21), cerebral infarction (I63), or stroke not specified as infarction or haemorrhage (I64). The true positive rate for Australian hospital records of cardiovascular separations is high (Jamrozik et al., 2001). The primary outcome of hospitalisation was selected, excluding events resulting in out-of-hospital treatment or death, to reflect the

contribution of depression and inflammation to severe events with ongoing morbidity. Thus, the current analyses bias toward the null and should be considered conservative.

Other variables: The baseline characteristics examined included self-reported values for age, gender, marital status, annual income before tax, employment, English as a first language, Short-Form 36 (SF-36) physical functioning subscale (Ware & Sherbourne, 1992), Kessler-10 (K-10) psychological distress (Kessler et al., 2002), smoking status, and self-reported disease history and medication use (some diseases prompted with specific questions including "angina", "heart attack", "stroke", others diseases free response; all medication free response). Alcohol consumption in the previous month was measured via a modified timeline follow-back method (Cumming & Mitchell, 1997; Skinner, 1982; Sobell et al., 1979) and was used to identify whether the participant consumed above contemporaneous Australian alcohol guidelines (>4 standard drinks per day for men, >2 standard drinks per day for women) (National Health and Medical Research Council, 2001). Participants also completed a previously validated semi-quantitative food frequency questionnaire (Smith, Mitchell, Reay, Webb, & Harvey, 1998), from which nutrient intakes, including percentage of energy from saturated fat, were determined using a custom-made nutrient analysis programme based on the NUTTAB 2006 database (Food Standards Australia New Zealand, 2006). An objective measure of physical activity was used, namely average step count per day via a pedometer worn over a week. BMI was calculated from height and weight, and waist-to-hip ratio was calculated from waist and hip circumference measurements assessed by research staff. Blood concentrations of total cholesterol and systolic blood pressure were also measured and reported.

Data analysis

Figure 1 depicts how the study sample size was derived from the original Hunter Community Study sample. Analyses were conducted on a sample free of cardiovascular

hospitalisation events at baseline, namely excluding people who self-reported “angina”, “heart attack” or “stroke” during the baseline survey. Additionally, analyses were restricted to participants who consented to linkage with hospitalisation records, were not using immunosuppressants, and had valid predictor data (CRP, IL-6, CES-D, age, gender, BMI or waist-to-hip ratio). We also excluded 134 individuals with CRP levels above 10mg/L as a conservative indicator of probable acute illness according to previously published guidelines (Clyne & Olshaker, 1999). Therefore, 1692 individuals remained (51% of original sample). We completed a supplementary sensitivity analysis where instead of clinical criterion of “probable acute illness”, the criterion for exclusion was statistical (values 3 standard deviations above the geometric mean; > 37mg/L in this sample; $N = 8$). For the analyses involving IL-6, we excluded 23 participants with high values of IL-6 (> 25pg/mL; 3 standard deviations above the geometric mean), and for analyses involving BMI, we excluded 4 participants with very high values (BMI > 50). Compared to excluded participants, participants who were included in the analyses were younger, more frequently married, more frequently unsafe drinkers, more frequently currently working and, consequently, higher income earners ($p > .05$). They also appeared somewhat healthier on some (although not all) measures, with lower CES-D and K-10 scores, greater average steps per day, lower BMI and waist-to-hip ratio, higher physical functioning scores, lower systolic blood pressure, fewer current and ex-smokers, less diabetes, less self-reported hypertension, and less use of cardiovascular medications, although more unsafe drinking ($p > .05$).

Figure 2 shows the model used to guide these analyses. The outcome for the analyses was the time to first cardiovascular hospitalisation (angina, myocardial infarction or cerebral infarction) occurring between the baseline survey and the end of follow-up. The key mediators CRP and IL-6 were log-transformed for analysis to account for non-normality. The key exposure,

CES-D score, also had some evidence of a skewed distribution which was not improved with transformation, so mediation analyses were undertaken using CES-D as a binary outcome with previously validated, established cut-off score of 16 (Beekman, et al., 1997) to indicate low vs. high depressive symptoms. Defining the predictor in this way leads to a readily interpretable result compared with using a skewed continuous predictor.

Firstly, descriptive statistics regarding baseline demographic and lifestyle factors for those who experienced and did not experience a cardiovascular hospitalisation during follow-up were compared via t-test or chi-square analyses. Secondly, we conducted Cox proportional-hazard regression models using these baseline characteristics to predict time until first cardiovascular hospitalisation after baseline or censoring at the end of the follow-up period (or death if known), controlling for age and gender. Age and gender were considered the most established confounders identified via directed acyclic graph (Hernán, Hernández-Diaz, & Robins, 2004). Because hazard ratios are interpreted as an instantaneous ratio of risk of event for a one unit increase in the predictor variable, waist-to-hip ratio was reported as a percentage rather than a ratio (waist circumference/hip circumference*100) to ease interpretation.

Finally, we conducted natural direct and indirect effects mediation analyses using the methods as described in Lange, Vansteelandt and Bekaert (2012) to model the natural direct relationship between depression and cardiovascular events and the natural indirect effect mediated via inflammation (as indicated by CRP or IL-6) or adiposity (BMI or waist-to-hip ratio). Details on the implementation of this procedure are available in the web appendix of Lange et al. (2012). Briefly, the associations between the exposure and mediator were analysed with linear models to obtain weights for the marginal structural model. The direct and indirect associations between exposure and outcome were modelled through Cox marginal structural models. A Cox model was selected to represent results as hazards, rather than parametric effect

sizes, as proportional hazard assumptions tested via Schoenfeld residuals were met. Overall fit was evaluated by examining Harrell's *C* concordance statistic. To compare the effect size of mediators, the proportion of the mediated effect was calculated by dividing the indirect coefficient by the sum of the direct and indirect coefficients and converted to a percentage.

Descriptive analyses were conducted using Stata SE/11 (StataCorp LP, USA) and mediation analyses were conducted using the R statistical language version 2.15 (R Foundation for Statistical Computing, Austria).

Results

Descriptive statistics

Across approximately 5140 person-years of risk, there were 47 cardiovascular hospitalisations (2.8% of sample); an incidence rate of 9.1 cardiovascular events per 1000 person-years. This is within the range of rates observed in other similarly aged cohorts (myocardial infarction: 6-23 in men and 3-11 in women; stroke: 4-20 in men and 2-17 in women) (National Heart Lung and Blood Institute, 2006). Comparing the incidence by CES-D depression status, for those without depression, incidence was 8.6 events per 1000 person-years, whereas for those with probable depression it was 13.1 per 1000 person-years. Higher depressive symptoms at baseline were also associated with a longer stay in hospital during admission, $\beta = 0.54$, SE = 0.21, $t(44) = 2.52$, $p = .016$.

Table 1 shows the baseline demographics, medical history and health behaviour for participants with and without cardiovascular events during follow-up. Participants who had a cardiovascular event were significantly older, and were more likely to be males, low income earners, have a self-reported history of diabetes and hypertension and current use of cardiovascular medications (beta-blockers, warfarin or ACE inhibitors). They also had elevated

levels of CRP and IL-6, had higher BMI and waist-to-hip ratio, took fewer steps per day, had lower total cholesterol, and a lower SF-36 physical health rating.

CRP, IL-6, BMI, waist-to-hip ratio, presence of diabetes and current use of cardiovascular medications were significant predictors of time to cardiovascular event (Table 1). Binary CES-D was a marginally significant predictor (p = .06). Adding CRP or IL-6 to a Cox model with age, gender and CES-D significantly improved the model, CRP: $\chi^2(1) = 3.83$, p = .05; IL-6: $\chi^2(1) = 5.03$, p = .02, and the effect size for CES-D remained stable. For the supplementary sensitivity analysis excluding participants due to statistical criterion (CRP over 3 standard deviations from the geometric mean), rather than criterion of possible acute illness, the hazard ratio for logCRP remained statistically significant (HR = 1.34, 95% CI 1.01, 1.78, p = .04).

Mediation analysis

Controlling for age and gender, baseline CES-D category was significantly associated with logCRP (β = 0.06, p = .01) and logIL-6 (β = 0.05, p = .04). In both mediation analyses, the indirect effects from binary CES-D category to cardiovascular hospitalisation via CRP or IL-6 were significant, whereas direct effects were not (Table 2). The proportion of effect mediated through CRP was 8.1% and through IL-6 was 10.9%. Concordance was equivalent for the models including CRP and IL-6, signifying that neither model outperformed the other in terms of fit (in each case, Harrell's C = .68; indicating correct identification of pairs of patients 68% of the time). Given the results observed in the Cox proportional-hazards models, we also examined BMI and waist-to-hip ratio as possible mediators between depression and cardiovascular disease. Controlling for age and gender, baseline CES-D category was significantly associated with BMI (β = 0.07, p < .01) and waist-to-hip ratio (β = 0.05, p < .01). The mediation results were similar to the results for the inflammatory markers, with significant indirect but not direct effects, although the proportion explained through the indirect effect was slightly smaller for BMI at 7.7%, and

equivalent to that of IL-6 for waist-to-hip ratio at 10.4% (Table 2; BMI Harrell's *C* = .70; waist-to-hip ratio Harrell's *C* = .68).

Discussion

The results of this study make an important contribution to the literature by examining the extent to which inflammatory markers explain some of the association between depression and cardiovascular events. In a community-dwelling sample of older people without a self-reported history of cardiovascular events, CRP and IL-6 were positively associated with risk of cardiovascular hospitalisation over time, after taking into account age and gender. Extending on previous studies, we demonstrated that inflammatory markers may at least partly explain the association between depression and cardiovascular events in a proposed mediation model. There was a significant indirect effect through inflammatory markers, whereas the direct effect from depression to cardiovascular events was non-significant and smaller in effect size than the model that only considered a direct effect. Thus, the indirect effect via inflammatory markers appears to be an important link in the depression-cardiovascular event association.

Although we analysed the current data as a possible causal network, our conclusions are cautious. Given that depression and inflammatory markers were measured contemporaneously, we could not examine the temporal precedence between the two in a true test of mediation. Nor do we know whether inflammatory markers and depressive symptoms have additive or multiplicative effects on risk of cardiovascular events over time. Furthermore, due to limitations of the dataset, we only examined one proposed causal model – that depression leads to inflammation, then cardiovascular events – although alternative causal models are likely. For instance, there is evidence that cardiovascular disease is associated with later depression, and that inflammation both precedes and follows depression (Fan, Strine, Jiles, & Mokdad, 2008;

Matthews, et al., 2010; Stewart, Rand, Muldoon, & Kamarck, 2009). Although not possible in the current study, establishing the temporal sequence between depression, inflammation and cardiovascular events by measuring each at multiple time points is an important future direction. Perhaps, rather than direction (or causality), it is more likely that there is interdependence and mutually reinforcing relationships between depression and cardiovascular disease (de Jonge & Roest, 2012).

Regardless of the direction of the associations, for these analyses we have considered a very simple causal model which places inflammation as a common causal link between depression and cardiovascular events. Given that the observed indirect effect for CRP and IL-6 in the current study was not overly large (8.1% and 10.9%, respectively), it is likely that other necessary biological and psychological mediators will help explain the association between depression and cardiovascular events. In this study, we explored the role of obesity and demonstrated that, like the inflammatory markers, BMI and waist-to-hip ratio produced significant indirect effects. The size of the indirect effect for waist-to-hip ratio was similar to that of the inflammatory markers, and was slightly smaller for BMI.

Considering the potential sources of inflammation may help elucidate the pathways between depression and cardiovascular disease. For instance, psychosocial stress may be a necessary precipitant and important aspect of the causal pathway, since stress is pro-inflammatory and a well-known precipitant of both depression and cardiovascular events. For instance, recent theories of depression suggest that real or imagined psychosocial stressors represented cortically activate inflammatory pathways and upregulate inflammatory gene expression, which results in the elevated circulating inflammatory mediators that cause cognitive, emotional and behavioural symptoms of depression (Raison & Miller, 2013; Slavich & Irwin, 2014). Aspects of unhealthy lifestyle, such as physical inactivity and poor quality “Western”

dietary patterns, may also be involved, since many of these aspects are pro-inflammatory and are associated with both depression and cardiovascular disease (Berk et al., 2013; Bonnet, et al., 2005; Hamer, 2012; O'Connor, et al., 2009). Alternatively, inflammation may be an indicator of underlying general somatic dysregulation, responsible for both depression and cardiovascular events (Hyland, 2010). Other suggested mechanisms that may be partly involved which were not captured in the current study include medication adherence, neuroendocrine deregulation, decreased heart rate variability or oxidative stress (Harrison, et al., 2013; Joynt, Whellan, & O'Connor, 2003; Lippi, Montagnana, Favaloro, & Franchini, 2009; Nemeroff & Goldschmidt-Clermont, 2012). Some of these factors are also associated with inflammation although they may also have independent physiological effects. Such factors should be explored systematically in future research. Existing studies suggest that even after adjusting for a range of factors including inflammation, lifestyle, and coagulation, there is still an association between depression and acute myocardial infarction (Janszky, Ahlbom, Hallqvist, & Ahnve, 2007). Perhaps there are as yet unknown mechanisms underlying the relationship.

Besides the restrictions in the causal model tested, the current results must be interpreted in light of several limitations. Although the observed event rate was similar to previous studies (National Heart Lung and Blood Institute, 2006), given the sample size there were few cardiovascular events, which limits the precision of our model. The outcome was limited to hospital recorded events, and not events that did not lead to hospital presentation (including death). Furthermore, history of cardiovascular events was only obtained through self-report. There were considerable missing data and so it is unclear whether the sample was representative of the broader older community. Some missing data were due to study design; for instance, provision of blood collection forms could only be provided to those people who could attend the physical clinic examination whereas the self-report measures were completed at the participant's

convenience via mailed form. Included participants were significantly younger, higher income earning and had better scores on some health measures including depressive symptoms (although not all health measures), and as such, the analyses of the current study may not represent a more depressed, physically unwell and potentially socio-economically disadvantaged segment of older persons. Although this may mean the relationships may not be representative of the broader community, the relationships observed are still representative of healthier community-dwelling older persons. Taken together, these study limitations mean that our findings are conservative; we have likely underestimated the true effects that may be observed if more unwell people were included in the study.

The present study demonstrates that inflammation may partly explain the association between depression and cardiovascular events. The effect was small, indicating that although there is a theoretical association between depression and inflammation, this does not translate to completely dependent risks. Nevertheless, the findings indicate that working to reduce inflammation may help prevent cardiovascular events and reduce depressive symptoms. Antidepressants may have anti-inflammatory effects, which could in turn reduce risk of cardiovascular events (Hiles, Baker, de Malmanche, & Attia, 2012a; Tynan et al., 2012). Furthermore, medications with anti-inflammatory effects such as statins and aspirin, which are often prescribed for primary or secondary prevention of cardiovascular events, are associated with reductions in depression (Hiles, Baker, Handley, de Malmanche, & Attia, under review; Pasco, Jacka, et al., 2010). There is also a role for intervening on aspects of unhealthy lifestyle and improving adherence to lifestyle management programs in people at risk of cardiovascular events, as aspects of unhealthy lifestyle factors such as adiposity are pro-inflammatory (Miller, et al., 2003; Shelton & Miller, 2010). For instance, modifications including exercise have been shown to reduce inflammatory markers, and inactivity is often a large contributor to risk of

cardiovascular event (Goldhammer et al., 2005; Hamer, et al., 2008; Whooley, et al., 2008; Woods, Vieira, & Keylock, 2006). These effects of physical inactivity may be mediated by BMI (Verdaet et al., 2004), so physical activity and diet with a view to improve adiposity may be particularly warranted. Furthermore, adhering to a lifestyle modification program may benefit the other psychological and physiological factors which may mediate the relationship between depression and cardiovascular diseases. Ultimately, this could provide a unified approach to managing mental and physical health.

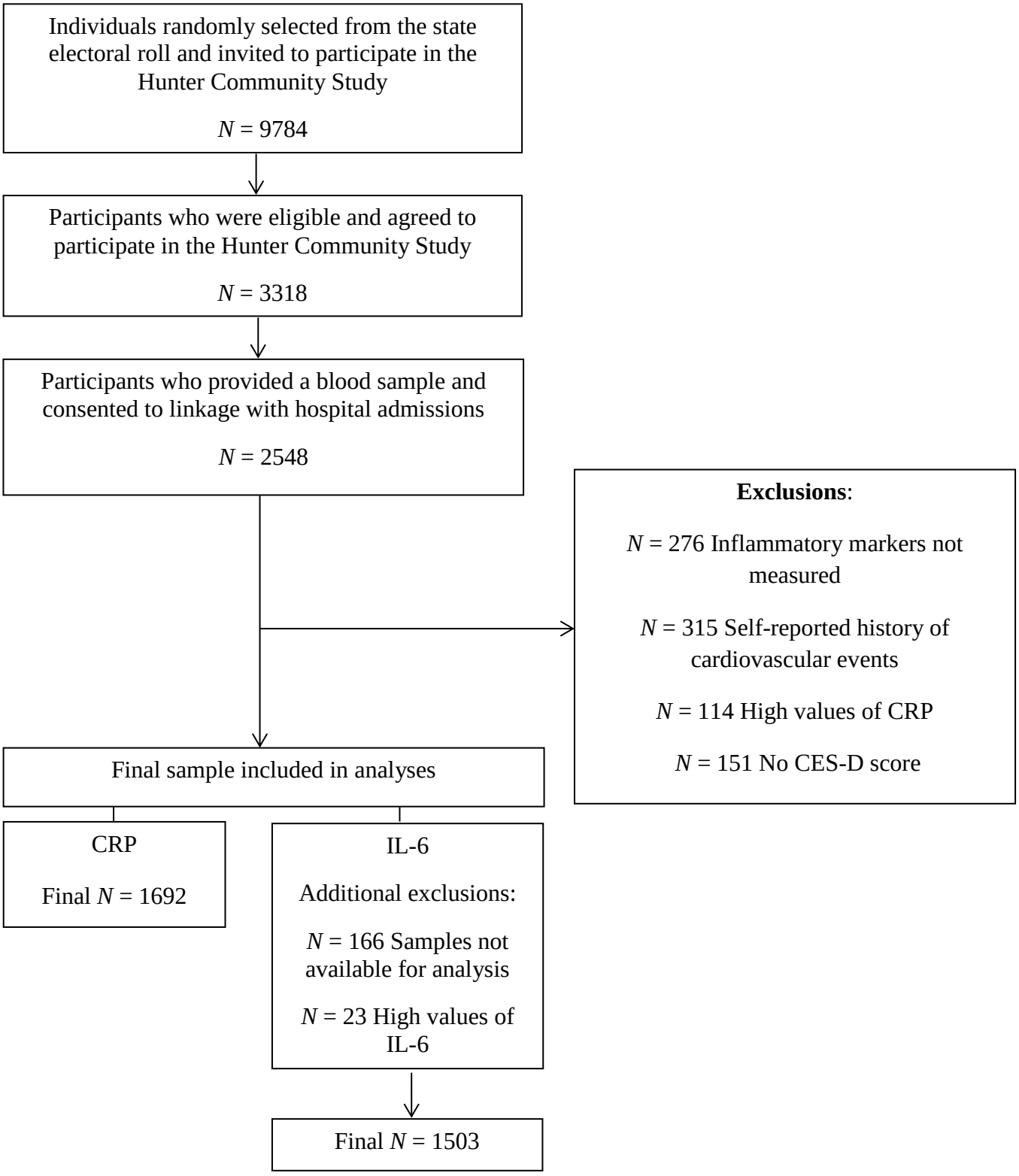

Figure 1. Flow chart indicating how the final sample was derived from the original Hunter Community Study cohort.

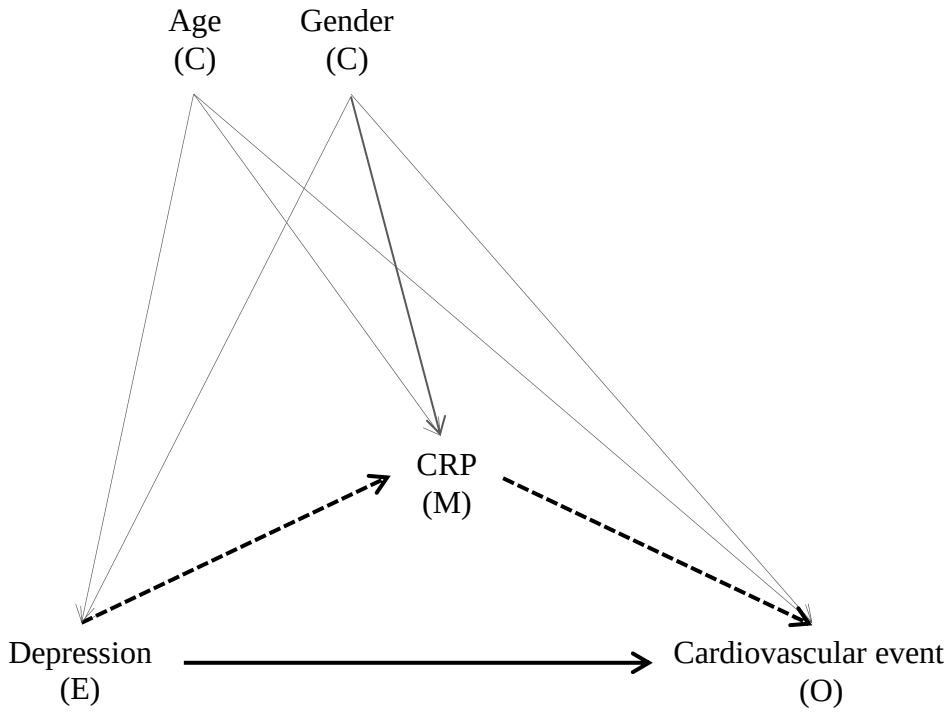

Figure 2. Simple proposed causal diagram of exposure (E; depression), mediator (M; C-reactive protein [CRP]), confounders (C; age and gender), and outcome (O; incident cardiovascular events of hospitalisation for angina, myocardial infarction or stroke). The model demonstrates the direct effect (DE) from depression to cardiovascular effects, and the indirect effect (IE) mediated via CRP. Interleukin-6, body mass index and waist-to-hip ratio were also examined as alternative mediators.

Table 1. Self-reported baseline demographic, health behaviour and medical history characteristics for participants with and without a cardiovascular event during follow-up, yet free of cardiovascular events at baseline, and Cox proportional hazard ratios (HR) for cardiovascular event, adjusted for age and gender (mean observation time 1109 days, median 937 days, range 636–1875 days).

	Baseline characteristic	Missing	Cardiovascular event (*N* = 47)	No cardiovascular event (*N* = 1645)	*p*	HR (95% CI) (adjusted for age and gender)			*p*
		N	Mean (SD)	Mean (SD)					
Demographic information	Age	0	**68.6 (7.2)**	**65.1 (7.1)**	**<.01**	**1.06**	**(1.02,**	**1.10)**	**<.01**
			N (%)	N (%)					
	Male	0	**35 (74.5)**	**762 (46.3)**	**<.01**	**3.56**	**(1.85,**	**6.87)**	**<.01**
	Married/de facto	34	35 (79.6)	1242 (77.0)	.69	1.08	(0.51,	2.31)	.84
	Employed (full/part-time)	30	10 (22.2)	498 (30.8)	.22	1.05	(0.47,	2.38)	.90
	Gross annual income above AU$40000	352	**7 (16.7)**	**473 (36.4)**	**.01**	0.45	(0.19,	1.05)	.07
	English first language spoken	85	39 (97.5)	1534 (97.9)	.86	0.79	(0.11,	5.76)	.81
			Mean (SD)	Mean (SD)					
Health information	K-10	3	14.7 (5.3)	14.1 (4.9)	.40	1.03	(0.98,	1.08)	.29
	logCRP	0	**0.9 (0.7)**	**0.7 (0.8)**	**.05**	**1.47**	**(1.02,**	**2.13)**	**.04**
	logIL-6	189	**0.9 (0.7)**	**0.6 (0.6)**	**<.01**	**1.72**	**(1.08,**	**2.72)**	**.02**
	Average steps per day (in thousands)	158	**6.0 (3.3)**	**7.1 (3.1)**	**.02**	0.91	(0.82,	1.01)	.09
	BMI	5	29.6 (3.8)	28.4 (4.6)	.08	**1.06**	**(1.00,**	**1.14)**	**.05**
	Waist-to-hip ratio (as %)	5	**94.3 (6.7)**	**88.9 (8.5)**	**<.01**	**1.05**	**(1.01,**	**1.10)**	**.02**
	Total cholesterol	7	**4.9 (1.0)**	**5.2 (1.0)**	**.03**	0.86	(0.63,	1.17)	.35
	% saturated fat intake	75	11.4 (3.6)	11.6 (3.3)	.70	0.97	(0.88,	1.06)	.46
	SF-36 physical health subscale	13	**70.1 (26.3)**	**77.6 (21.9)**	**.02**	0.99	(0.98,	1.00)	.07
	Systolic blood pressure	3	137.5 (19.2)	138.1 (41.4)	.93	1.00	(0.99,	1.01)	.75
			N (%)	N (%)					

	CES-D ≥ 16	0	8 (17.0)	192 (11.7)	.26	2.12	(0.97,	4.60)	.06
	CES-D ≥ 16 or current antidepressant use	0	10 (21.3)	302 (18.4)	.61	1.51	(0.75,	3.06)	.25
	BMI ≥ 25	5	**44 (93.5)**	**1276 (77.8)**	**.01**	**3.55**	**(1.09,**	**11.57)**	**.04**
	Current smokers	39	4 (8.9)	105 (6.5)	.53	1.59	(0.56,	4.48)	.38
	Previous smokers	38	25 (56.8)	693 (43.0)	.07	1.54	(0.83,	2.85)	.17
	Alcohol consumption above guidelines*	188	9 (25.0)	282 (19.2)	.39	1.30	(0.60,	2.80)	.51
Self-reported health history	Depression/anxiety	59	4 (9.5)	322 (20.2)	.09	0.60	(0.21,	1.69)	.33
	Diabetes	59	**10 (23.8)**	**142 (8.9)**	**<.01**	**2.42**	**(1.19,**	**4.96)**	**.02**
	Hypertension	50	24 (54.6)	663 (41.5)	.08	1.60	(0.88,	2.92)	.12
	Current use of antidepressants	430	4 (11.1)	158 (12.9)	.75	0.98	(0.35,	2.78)	.97
	Current use of statins	430	13 (36.1)	383 (31.2)	.54	1.15	(0.58,	2.27)	.69
	Current use of beta-blockers, warfarin, or ACE inhibitors	430	**24 (66.7)**	**576 (47.0)**	**.02**	**2.07**	**(1.03,**	**4.17)**	**.04**

*Australian National Health and Medical Research Council alcohol use guidelines 2001 (contemporaneous with study): >4 standard drinks per day for men, >2 standard drinks per day for women.

Abbreviations:

ACE inhibitor: angiotensin-converting-enzyme inhibitor

BMI: Body mass index

CES-D: Centre for Epidemiologic Studies Depression Scale

CRP: C-reactive protein

IL-6: interleukin-6

K-10: Kessler-10

SF-36: short-form 36

Table 2. Mediation analysis for the natural direct effect from CES-D category to later cardiovascular hospitalisations, and the natural indirect effect mediated via C-reactive protein (CRP), interleukin (IL)-6, body mass index (BMI) or waist-to-hip ratio within strata of confounders age and gender.

	Direct effect HR (95% CI)			% of effect direct	Indirect effect HR (95% CI)			% of effect indirect
Depression (via CRP)	1.94	(0.86,	4.38)	91.9	1.06	(1.01,	1.11)	8.1
Depression (via IL-6)	1.61	(0.63,	4.09)	89.1	1.06	(1.00,	1.12)	10.9
Depression (via BMI)	2.02	(0.90,	4.55)	92.3	1.06	(1.00,	1.12)	7.7
Depression (via waist-to-hip ratio)	1.91	(0.85,	4.31)	89.6	1.08	(1.01,	1.15)	10.4

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