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CRP 1846G>A polymorphism increases risk of frailty

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ABSTRACT

Background: Frailty is a syndrome characterized by diminished ability to re-establish homeostasis in response to stress. We hypothesized that deficient allostatic responses to physiological challenges may predispose to frailty, that C-reactive protein (CRP) and its genetic determinants may be a measure of the integrity of the allostatic response, and that genetic determinants of the allostatic response determine the risk of frailty.
Methods: Cross-sectional study of 3778 community-dwelling older men identified by random sampling of the Australian electoral roll. Explanatory variables included demographic, clinical, lifestyle behaviors, serum high-sensitivity CRP (hsCRP), and *CRP* 1444C>T and 1846G>A genotypes. These respective polymorphisms increase and decrease the basal concentration of hsCRP. The study outcome was frailty defined by a score of ≥ 4 on the FRAIL scale.
Results: The mean age of participants was 77.1 years (SD: 3.6) and frailty was present in 196 (5.2%). The serum concentration of hsCRP was higher in frail than non-frail men ($p < 0.001$), but levels varied according to genotypes. The odds of frailty increased progressively from GG to GA and AA genotypes of the *CRP*1846G>A gene ($z = 3.93$, $p < 0.001$), and were 2.43 (95%CI = 1.62–3.67) times greater in men with *CRP*1846G>A AA compared with GG genotypes. The *CRP* 1444C>T was not associated with frailty.
Conclusion: Frail people have raised serum concentrations of CRP, presumably in response to the stress of underlying cause(s). However, frail individuals carrying the *CRP*1846G>A polymorphism seem less able to mount an efficient allostatic response, which may underpin their increased odds of frailty.

1. Introduction

Frailty is a clinical syndrome characterized by diminished ability to manage stressors successfully [1]. It is particularly common in older age, and its presence is associated with functional decline and increased risk of major health events and death [2]. The mechanisms that contribute to the development of frailty are not entirely clear, but they ultimately disrupt the processes that maintain the stability of the physiological milieu of the organism, also known as homeostasis [3]. Internal and external factors are relentless in their challenge to homeostasis and their presence requires an appropriate acute response of the organism that minimizes their impact. Such a response is known as allostasis. Allostatic responses allow biological systems to address and adapt to real or perceived challenges, such as infection or tissue damage [4]. An inefficient or maladaptive response to physiological stress may contribute to extend or perpetuate damage to the organism, thereby compromising its ability to re-establish a stable homeostatic state over time (i.e., frailty) [5].

Inflammatory markers, such as C-reactive protein (CRP), are acute phase response proteins induced during inflammatory states that rise as much as 2000 fold during the first 24–48 h after the onset of tissue injury or inflammation [6] (i.e., CRP can be considered a marker of allostatic response). Therefore, it is not surprising that CRP concentrations are raised in frail people [7], and that moderately elevated levels are also associated with incident frailty [8].

The precise physiological functions of CRP remain uncertain, although currently available evidence suggests it plays a key role

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in the recognition of foreign pathogens and of damaged cells of the host and contributes to triggering the humoral and cellular responses that ultimately lead to their clearance [9]. CRP has a calcium-dependent binding specificity for phosphocholine (PCh), which is present in the outer layer of most biological membranes, and for several nuclear constituents such as histones and ribonucleoprotein particles [9,10]. Bound CRP is recognized by C1q and initiates cleavage and activation of C3 and C4 through the classical complement pathway [9,11]. In addition, CRP has high affinity for phagocytic receptors [12] and seems to promote phagocytosis [9].

Genetic variation also affects the concentration of CRP [13–15]. For example, the CRP1444C>T variant increases basal and stimulated CRP levels [16], whereas the CRP1846G>A variant has the opposite effect [13]. We have previously shown that carriers of the CRP1846G>A polymorphism fail to mount an effective inflammatory response to deteriorating health, and this increases their risk of developing depression [17].

We designed this study to determine if the serum concentration of CRP and *CRP* polymorphisms are associated with frailty. We hypothesized that the prevalence of frailty would be higher amongst carriers of the CRP1846G>A polymorphism, as their ability to mount effective allostatic responses in the face of stress would be reduced compared with carriers of the wild genotype.

2. Methods

2.1. Participants

Our analyses are based on a community-derived sample of older men living in Perth, Western Australia, who collectively constitute the Health in Men Study (HIMS) cohort. Details regarding enrolment and assessment procedures have been described elsewhere [18]. Briefly, 12,203 men aged 65 years or older were recruited via random sampling from the Australian electoral roll between 1996 and 1998, enrolment to vote being compulsory for all adult Australian citizens. During the years 2001–2004 those men who were still alive were contacted and invited to complete a follow-up assessment and donate a fasting blood sample ($n = 9718$). This report refers to 3778 participants who agreed do donate a blood sample for biochemical and genetic analysis, and provided valid information to establish the presence of frailty.

The Ethics Committee of the University of Western Australia approved the study protocol and participants provided written informed consent. All procedures in this study complied with the Helsinki declaration on human rights (http://chnm.gmu.edu/1989/items/show/245).

2.2. Outcome of interest

We based our definition of frailty on the FRAIL scale [19,20]. The scale consists of five domains – fatigue (0/1), resistance (0/1), ambulation (0/1), illness (0/1), and loss of weight (0/1) – which we assessed using self-reported information obtained from participants. We used items of the SF-36 Health Survey [21] to assess symptoms of fatigue (worn out or feeling tired most of the time), resistance (inability to climb a flight of stairs) and ambulation (inability to walk 100 m). Men who reported 6 or more of the following illnesses were given a score of 1 for 'illness': arthritis, diabetes, angina or myocardial infarction, hypertension, stroke, asthma, chronic bronchitis, emphysema, osteoporosis, colorectal cancer, skin cancer, depression or anxiety disorder, Alzheimer's disease or other dementia, or leg ulcers. Participants scored positive for weight loss if they reported having lost weight (in Kg) between the assessments.

We validated this approach by investigating the survival of participants according to their score on the FRAIL scale, and showed that those with a score of 4 or more have much lower 7-year survival than those with lower scores (most frail group) [22]. Hence, we considered our participants 'frail' if they had a total score of 4 or more on the FRAIL scale. The scale has been validated on an independent sample of older women [23].

2.3. Explanatory variables

Consenting men were asked to complete a self-report questionnaire that included items assessing demographic and clinical information. They recorded the date and place of their birth, and we calculated their age as the difference in years between the date of the assessment (which included the blood tests) and their date of birth. Participants also reported whether they had completed high school education (yes/no), whether they had ever smoked (yes/no), and whether they were still smoking at the time of assessment (every day/not every day/not at all). Men who answered 'every day' or 'not every day' were classified as current smokers.

In addition, participating men completed the SF-36 Health Survey [21]. For the purposes of this study, the analyses were limited to the physical (PCS) and mental health component summary (MCS) measures. The mean PCS and MCS for the Australian population is 50, with a standard deviation of 10 [24]. We used the PCS and MCS scores as proxy measures of physical and mental health.

Information about alcohol consumption and physical activity was gathered during the 1996–1998 assessment (about 5 years before the collection of blood samples). Participants recorded the number of standard drinks that they usually consumed each day of the week, which we then grouped into <14, 14–27, or 28 or more drinks in a usual week. In addition, these men recorded the total number of minutes they engaged in moderate to vigorous physical activities (that made them breathe harder, or puff and pant) during a usual week. We considered that men were physically active if they reported 150 min or more of moderate to vigorous physical activity per week.

2.4. Biochemical and genetic analyses

Blood samples were collected between 08:00 and 10:30 am following overnight fasting. Serum was prepared immediately following phlebotomy, stored on ice and assayed within 3 h. Biochemical assays and genetic analyses were performed in the Department of Biochemistry, PathWest, Royal Perth Hospital, Western Australia. We measured the serum concentration of CRP with a high-sensitivity particle-enhanced immunonephelometry system on a BNII analyzer (hsCRP; Dade Behring, MN, USA). The interassay coefficient of variation (CV) for this test ranges from 4 to 7%, and a serum concentration of 3 mg/L or greater is associated with tissue damage or inflammation [25].

Genomic DNA was extracted from the buffy coat fraction of centrifuged blood using a standard triton X-100 method. CRP genotyping was carried out using 5′-nuclease assays (TaqMan) with fluorescent single nucleotide peptide (SNP) allelic discrimination by means of an ABI 7900HT (Applied Biosystems, Foster City, USA) using primers and probes designed by Applied Biosystems for *CRP*1444C>T (rs1130864) and 1846G>A (rs1205). The distribution of these SNPs within the *CRP* gene region has been described by others [26,27].

2.5. Statistical analyses

Data were managed and analyzed with the statistical package Stata release 10.0 (StataCorp, College Station, Texas). We grouped participants according to their frailty status (yes/no), and used

logistic regression to calculate the odds of frailty (plus 95% confidence intervals, 95%CIs) associated with the measured exposures: age, place of birth, education, smoking, alcohol use, physical activity, PCS and MCS group scores, and the serum concentration of hsCRP (<3, 3–9.9 and ≥10 mg/L).

We determined if the distribution of alleles at *CRP* SNPs rs1130864 and rs1205 were in equilibrium according to the Hardy–Weinberg test (exact method), and then investigated if the serum concentration of hsCRP changed according to the genotype of participants. Finally we used logistic regression to examine the association between these common *CRP* polymorphisms and frailty, and subsequently determined the serum concentration of hsCRP for frail and non-frail men according to their *CRP* genotype. As hsCRP was positively skewed, we transformed these values into binary logs by dividing the natural log transformed value of hsCRP by the natural log of 2. Logistic regression performed using these values produced the odds ratio of frailty for a doubling of hsCRP.

3. Results

The study sample consisted of 3778 men, of whom 196 (5.2%) fulfilled the study criteria for the diagnosis of frailty. Frail men were older than non-frail participants (79.2 ± 3.7 vs. 76.9 ± 3.6, $t = 8.76$, df = 3776, $p < 0.001$). Table 1 summarizes the demographic, lifestyle and biochemical characteristics of participants. The odds of frailty were lower amongst men who had completed high school or who were physically active. In contrast, the odds of frailty were higher amongst past or current smokers, and increased as health related quality of life scores decreased (both PCS and MCS). Frail men had higher serum concentration of hsCRP than non-frail participants (geometric mean ± SD: 3.1 ± 3.1 vs. 2.0 ± 2.8; $t = 5.96$, df = 3774, $p < 0.001$), and the odds of frailty increased 32% with the doubling of hsCRP (OR = 1.32, 95%CI = 1.20–1.44). The proportion of men with high (>3 mg/L) or very high hsCPR (>10 mg/L) was higher amongst frail than non-frail participants (Table 1).

We examined if distribution of the CRP1444C>T and CRP1846G>A polymorphisms were in equilibrium, as determined by the Hardy–Weinberg test. The results of these analyses are summarized in Table 2 and show that the distribution of both SNPs was in Hardy–Weinberg equilibrium.

The serum concentration of hsCRP increased from the major to the minor homozygote CRP1444C>T polymorphism and decreased from the major to the minor homozygote CRP1846G>A polymorphism (Table 2). Table 3 shows the distribution of frailty according to CRP1444C>T and CRP1846G>A genotypes. Men homozygote for the minor allele of the CRP1846G>A polymorphism had 2.43 (95%CI = 1.62–3.67) greater odds of being frail than their homozygote wild counterparts. The odds of frailty increased progressively from the GG to the GA and then the AA genotypes ($z = 3.93$, $p < 0.001$).

Fig. 1 depicts the serum concentration of hsCRP according to common polymorphisms of the CRP gene amongst frail and non-frail men. Whilst the presence of frailty was associated with higher hsCRP in the sample (Table 1 and above), carriers of the CRP1846G>A polymorphism had lower hsCRP than non-carriers, and this decline was particularly pronounced amongst those who were homozygote for the minor allele. In contrast, the serum concentration of hsCRP increased amongst carriers of the CRP1444C>T polymorphism, particularly for the frail homozygote carriers of the minor allele. Men with the CRP1444C>T TT genotype who were frail had a serum concentration of hsCRP 2.3 mg higher than frail men with the CRP1846G>A AA genotype ($t = 6.23$, df = 143, $p < 0.001$; after natural logarithmic transformation).

As the results of a previous study had shown that the CRP1846G>A polymorphism was associated with depression in later life [17], we completed a series of posthoc analyses to clarify if the observed association with frailty had been confounded by the presence of prevalent depression. The adjusted odds of frailty associated the CRP1846G>A polymorphism were 1.38 (95%CI = 0.99–1.93, $z = 1.89$, $p = 0.059$) and 2.34 (95%CI = 1.52–3.60, $z = 3.88$, $p < 0.001$) for the minor heterozygote and homozygote genotypes. Finally, we repeated the analyses investigating the association between the CRP1846G>A polymorphism and frailty after excluding men with serum concentration of hsCRP ≥ 10 mg/L to minimize possible bias caused by the presence of acute illness [28]. The associations remained unchanged: the odds ratio of frailty was 1.23 (95%CI = 0.86–1.75, $z = 1.14$, $p = 0.256$) and 2.70 (95%CI = 1.76–4.13, $z = 4.56$, $p < 0.001$) for heterozygote and minor homozygote CRP1846G>A men.

4. Discussion

The results of this study confirm that common polymorphisms of the CRP gene contribute to modulate the basal concentration of hsCRP, which is higher amongst carriers of the CRP1444C>T polymorphism and lower in carriers of the CRP1846G>A polymorphism. As predicted, the odds of frailty were nearly 2.5 times greater amongst older Australian men homozygote for the minor compared with the major allele of the CRP1846G>A polymorphism.

4.1. Limitations of the study

This survey has the merit of having used a large and well-established community-representative sample of older men for whom relevant clinical, genetic and biochemical information was available [18]. We accept, however, that we cannot infer causality between the factors under investigation because of the cross-sectional nature of the study. There is also evidence that our older men who elected not to take part in the survey were less healthy (and possibly more frail) than those who did [29]. This would have biased our results towards a healthier sample and diminished our ability to investigate the associations between frailty, serum concentration of CRP and *CRP* polymorphisms. This type of bias is associated with decreased power but not with type I error. In addition, we used a validated scale and a demanding cut-point to establish the presence of frailty in this sample. We recognize, however, that our definition of frailty was not based on a formal assessment, as suggested by some authors [1,30]. In addition, our study included older men only and the findings may not necessarily apply to women. Another limitation of our approach is that we limited our analyses to two SNPs of the *CRP* gene and this does not provide a complete picture of the possible haplotypes that control its expression. However, our focus was on two previously well described SNPs associated with high and low serum concentration of CRP [16] with the specific aim of teasing out the effects of CRP on frailty.

We also acknowledge that the polymorphisms that we investigated in the two SNPs of the *CRP* gene are related to hsCRP (one increasing and the other decreasing its serum concentration) but not to frailty (i.e., the CRP1444C>T polymorphism increases the serum concentration of hsCRP but does not reduce the odds of frailty). This may indicate that the study was not sufficiently powered to demonstrate the association between the CRP1444C>T polymorphism and frailty, or that the association between the CRP1846G>A polymorphism and frailty is either not causal or is affected by pleiotrophy. Moreover, the serum concentration of hsCRP reported in this study refers to the basal concentration of the sample, so that implications for our participants' ability to mount an effective allostatic response are inferred rather than measured directly.

Table 1
Demographic, lifestyle and clinical characteristics of older men according to frailty status.

		Frail		Odds ratio (95%CI)	*p*-Value
		No*N* = 3582*n* (%)	Yes*N* = 196*n* (%)		
Demographic features					
Age (in years)	70–74	1831 (51.1)	47 (24.0)	1 (Reference)	
	75–79	1155 (32.2)	74 (37.8)	2.50 (1.72–3.62)	<0.001
	80–84	499 (13.9)	63 (32.1)	4.92 (3.33–7.27)	<0.001
	85+	97 (2.7)	12 (6.1)	4.82 (2.48–9.38)	<0.001
Born overseas		1351 (37.8)	61 (31.1)	0.75 (0.55–1.02)	0.064
High school education		1756 (49.0)	68 (34.7)	0.55 (0.41–0.75)	<0.001
Lifestyle					
Smoking	Never	1219 (34.0)	37 (18.9)	1 (Reference)	
	Past	2177 (60.8)	142 (72.4)	2.15 (1.49–3.11)	<0.001
	Current	185 (5.2)	17 (8.7)	3.03 (1.67–5.49)	<0.001
Drinking[a]	<14 drinks/week	2442 (71.7)	126 (66.0)	1 (Reference)	
	14–27 drinks/week	708 (20.8)	43 (22.9)	1.18 (0.82–1.68)	0.370
	28+ drinks/week	255 (7.5)	19 (10.1)	1.44 (0.88–2.38)	0.149
Physically active[a]		846 (23.6)	19 (9.7)	0.35 (0.21–0.56)	<0.001
Health related quality of life					
PCS score	50+	887 (24.9)	2 (1.0)	1 (Reference)	
	40–49.9	1322 (37.2)	10 (5.1)	3.71 (0.73–15.35)	0.119
	30–39.9	898 (25.2)	43 (22.2)	21.24 (5.13–87.93)	<0.001
	<30	451 (12.7)	139 (71.6)	136.69 (33.69–554.54)	<0.001
MCS score	50+	2908 (81.7)	96 (49.5)	1 (Reference)	
	40–49.9	457 (12.8)	56 (28.9)	3.71 (2.63–5.24)	<0.001
	30–39.9	154 (4.3)	32 (16.5)	6.29 (4.09–9.69)	<0.001
	<30	39 (1.1)	10 (5.1)	7.76 (3.77–16.02)	<0.001
CRP					
High sensitivity CRP (mg/L)	<3	2463 (68.8)	99 (50.5)	1 (Reference)	
	3–9.9	898 (25.1)	68 (34.7)	1.88 (1.37–2.59)	<0.001[b]
	10+	219 (6.1)	29 (14.8)	3.29 (2.13–5.10)	<0.001[c]
Doubling of hsCRP				1.31 (1.20–1.44)	<0.001[d]

95%CI, 95% confidence interval of the odds ratio (OR). PCS, physical component score of the SF-36 Health Survey; MCS, mental component score of the SF-36 Health Survey; hsCRP, high sensitivity C-reactive protein concentration.

[a] Data collected 5 years before the assessment of frailty.

[b] OR = 1.56, 95%CI = 1.09–2.26, $p = 0.017$; adjusted for age group, education, place of birth, smoking, physical activity, and PCS and MCS grouping.

[c] OR = 2.01, 95%CI = 1.21–3.35, $p = 0.007$; adjusted for age group, education, place of birth, smoking, physical activity, and PCS and MCS grouping.

[d] OR = 1.15, 95%CI = 1.03–1.27, $p = 0.010$; adjusted for age group, education, place of birth, smoking, physical activity, and PCS and MCS grouping.

Table 2
Frequency distribution and respective serum concentration of hsCRP (geometric mean) according to two common polymorphisms of the *CRP gene*.

CRP polymorphisms	Major homozygote	Heterozygote	Minor homozygote	Minor allele frequency (SE)	HWET *p*-value
Allele frequency, n (%)					
1444C>T	1822 (48.7)	1569 (41.9)	352 (9.4)	0.305 (0.005)	0.589
1846G>A	1664 (44.0)	1699 (45.0)	415 (11.0)	0.335 (0.005)	0.559

CRP polymorphisms	Major homozygote	Heterozygote	Minor homozygote	*F*-Statistic	*p*-Value
Serum concentration of hsCRP, geometric mean (95%CI)					
1444C>T	1.9 (1.8–2.0)	2.1 (2.0–2.2)	2.5 (2.2–2.8)	13.83	<0.001
1846G>A	2.3 (2.2–2.4)	1.8 (1.7–1.9)	1.6 (1.4–1.7)	33.62	<0.001

HWET, Hardy–Weinberg equilibrium exact test probability value (*p*-value). SE, standard error. hsCRP, high sensitivity C-reactive protein. *F*-Statistic derived from oneway analysis of variance. 95%CI, 95% confidence interval of the geometric mean.

Table 3
Frequency distribution and odds ratio of frailty associated with common CRP polymorphisms.

	Frail		Odds ratio (95%CI)	*p*-Value
	No *N* = 3582 *n* (%)	Yes *N* = 196 *n* (%)		
CRP polymorphisms				
1444C>T				
CC	1717 (48.4)	105 (53.8)	1 (Reference)	
CT	1496 (42.2)	73 (37.4)	0.80 (0.59–1.08)	0.149
TT	335 (9.4)	17 (8.7)	0.83 (0.49–1.40)	0.487
1846G>A				
GG	1596 (44.6)	68 (34.7)	1 (Reference)	
GA	1610 (44.9)	89 (45.4)	1.30 (0.94–1.79)	0.114
AA	376 (10.5)	39 (19.9)	2.43 (1.62–3.67)	<0.001

CRP, C-reactive protein; 95%CI, 95% confidence interval of the odds ratio.

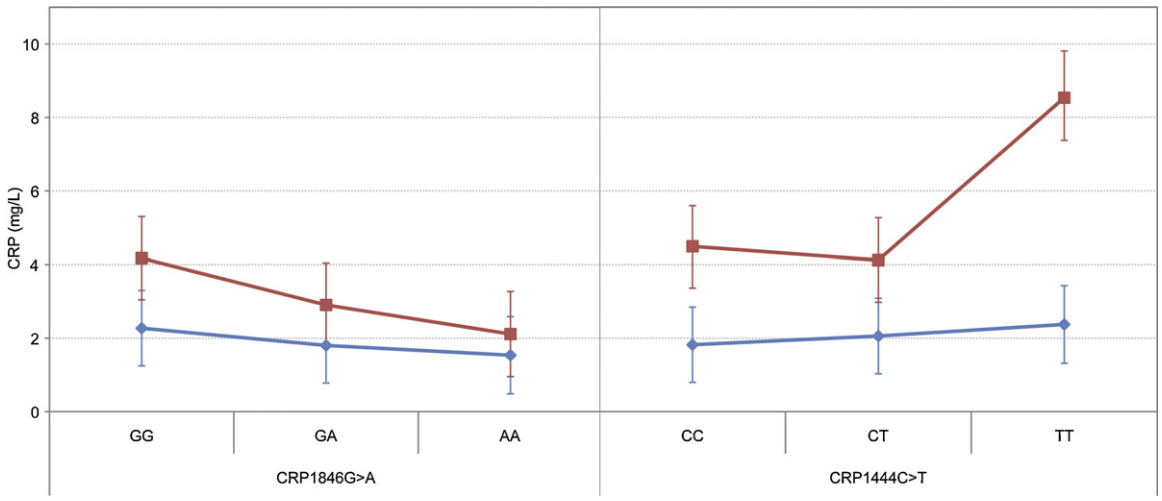

Fig. 1. Serum concentration of high sensitivity CRP (hsCRP, geometric mean in mg/L) according to frailty status (red square = frail, blue diamond = not frail) and common polymorphisms of the CRP gene: 1846G>A (left panel) and 1444C>T (right panel). The whiskers represent the error bars of the serum concentration of hsCRP for each individual genotype. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

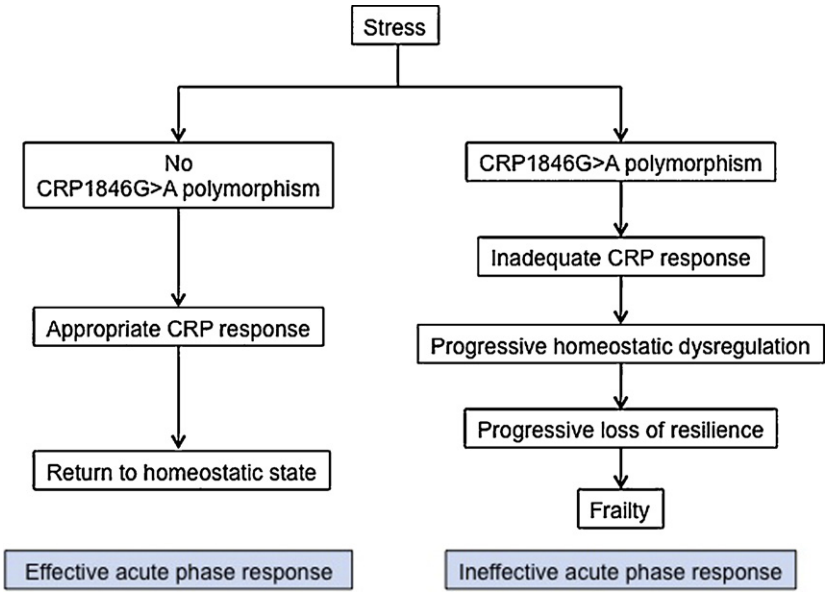

Fig. 2. The figure illustrates the potential pathway linking exposure to stress to the development of frailty (on the right hand side). In this model, acute phase response is compromised by the presence of the CRPG1846G>A polymorphism, which hinders the effective resolution of acute stress and increases the risk of frailty. Frailty is a state associated with progressive and persistent homeostatic dysregulation and decreased resilience.

4.2. Interpretation of findings

Our results suggest that failure to raise the serum concentration of CRP appropriately as a response to injury contributes to increase the risk of frailty in older Australian men. They are consistent with the possibility that carriers of the CRP1846G>A polymorphism produce a deficient CRP response to injury, which in turn may perpetuate immune and inflammatory reactions that ultimately lead to the ongoing disruption of homeostatic mechanisms. In this model, the CRP1846G>A polymorphism would contribute to the development of frailty by diminishing the individual's ability to respond efficiently to stress and injury (Fig. 2).

Over 10 years ago, McEwen [5] suggested that organisms react to real or perceived challenges in two ways: (1) they mount an allostatic response that initiates a complex adaptive pathway (for example, to combat an infection), (2) they turn off the allostatic response when the threat is no longer present. Whilst the acute response is commonly adaptive, chronic allostatic load may result in damage to the organism because of repeated hits, lack of adaptation (i.e., decreased ability to turn off the allostatic response), prolonged (i.e., no recovery) or inadequate responses. McEwen suggested that a flattened or inadequate acute allostatic response to insult leads to compensatory hyperactivity of other stress-related mediators (such as cytokines) [31], and this could lead to the development of frailty. However, such an explanation can only be considered speculative at this stage, as our study lacked supportive data to test the various steps involved in the allostatic model directly.

4.3. Conclusion

A frail individual is at the limit of his or her ability to cope with stressors. Our results demonstrate that the CRP1846G>A polymorphism reduces basal hsCRP and increases the odds of frailty

in older Australian men. People with such a genetic predisposition may require greater medical assistance than those without to overcome the numerous physiological challenges to homeostasis that characterize older age.

Contributors

Almeida had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept, design and data analysis were done by Almeida. Acquisition of data was done by Almeida, Norman, van Bockxmeer, Hankey and Flicker. Almeida, Norman, van Bockxmeer, Hankey and Flicker Interpreted the data. Almeida drafted the manuscript. Almeida, Norman, van Bockxmeer, Hankey and Flicker did the critical revision of the manuscript for important intellectual content.

Competing interests

None of the investigators have a conflict of interest to report.

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The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

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References

[1] Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A: Biol Sci Med Sci 2009;64:1049–57.
[2] Rockwood K, Howlett SE, MacKnight C, et al. Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian study of health and aging. J Gerontol A: Biol Sci Med Sci 2004;59:1310–7.
[3] Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992;267:1244–52.
[4] McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann NY Acad Sci 1998;840:33–44.
[5] McEwen BS. Protective and damaging effects of stress mediators. New Engl J Med 1998;338:171–9.
[6] Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem 2004;279:48487–90.
[7] Hubbard RE, O'Mahony MS, Calver BL, Woodhouse KW. Plasma esterases and inflammation in ageing and frailty. Eur J Clin Pharmacol 2008;64:895–900.
[8] Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. Clin Endocrinol (Oxf) 2005;63:403–11.
[9] Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol 2001;38:189–97.
[10] Robey FA, Jones KD, Steinberg AD. C-reactive protein mediates the solubilization of nuclear DNA by complement in vitro. J Exp Med 1985;161:1344–56.
[11] Kaplan MH, Volanakis JE. Interaction of C-reactive protein complexes with the complement system. I. Consumption of human complement associated with the reaction of C-reactive protein with pneumococcal C-polysaccharide and with the choline phosphatides, lecithin and sphingomyelin. J Immunol 1974;112:2135–47.
[12] Marnell LL, Mold C, Volzer MA, Burlingame RW, Du Clos TW. C-reactive protein binds to Fc gamma RI in transfected COS cells. J Immunol 1995;155:2185–93.
[13] Crawford DC, Sanders CL, Qin X, et al. Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey. Circulation 2006;114:2458–65.
[14] Lange LA, Carlson CS, Hindorff LA, et al. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. JAMA 2006;296:2703–11.
[15] Verzilli C, Shah T, Casas JP, et al. Bayesian meta-analysis of genetic association studies with different sets of markers. Am J Hum Genet 2008;82:859–72.
[16] Brull DJ, Serrano N, Zito F, et al. Human CRP gene polymorphism influences CRP levels: implications for the prediction and pathogenesis of coronary heart disease. Arterioscler Thromb Vasc Biol 2003;23:2063–9.
[17] Almeida OP, Norman PE, Allcock R, et al. Polymorphisms of the CRP gene inhibit inflammatory response and increase susceptibility to depression: the Health in Men Study. Int J Epidemiol 2009;38:1049–59.
[18] Norman PE, Flicker L, Almeida OP, Hankey GJ, Hyde Z, Jamrozik K. Cohort profile: the Health in Men Study (HIMS). Int J Epidemiol 2009;38:48–52.
[19] Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. J Am Med Dir Assoc 2008;9:71–2.
[20] Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A. task force on frailty assessment of older people in clinical practice. J Nutr Health Aging 2008;12:29–37.
[21] Ware JE, Kosinski M, Gandek B. SF-36 Health Survey: manual & interpretation guide. Lincoln, RI: QualityMetric Incorporated; 2000.
[22] Hyde Z, Flicker L, Almeida OP, et al. Low free testosterone predicts frailty in older men: the Health in Men Study. J Clin Endocrinol Metab 2010;95:3165–72.
[23] Lopez D, Flicker L, Dobson A. Validation of the FRAIL scale in a cohort of older Australian women. J Am Geriatr Soc; in press.
[24] ABS. National Health Survey: SF-36 population norms, Australia. Canberra: Australian Bureau of Statistics; 1995.
[25] Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
[26] Carlson CS, Aldred SF, Lee PK, et al. Polymorphisms within the C-reactive protein (CRP) promoter region are associated with plasma CRP levels. Am J Hum Genet 2005;77:64–77.
[27] Timpson NJ, Lawlor DA, Harbord RM, et al. C-reactive protein and its role in metabolic syndrome: mendelian randomisation study. Lancet 2005;366:1954–9.
[28] Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. New Engl J Med 2004;350:1387–97.
[29] Almeida OP, Yeap BB, Hankey GJ, Jamrozik K, Flicker L. Low free testosterone concentration as a potentially treatable cause of depressive symptoms in older men. Arch Gen Psychiatry 2008;65:283–9.
[30] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A: Biol Sci Med Sci 2001;56:M146–56.
[31] McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin Neurosci 2006;8:367–81.