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Running Head: Blunted cardiovascular reactivity

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Abstract

The reactivity hypothesis implicates exaggerated cardiovascular reactions to acute psychological stress in the development of hypertension and other cardiovascular disease outcomes. However, cardiovascular reactivity has also been suggested as a mediator between a variety of psychosocial and behavioural risk factors and cardiovascular disease. Data from various analyses of the West of Scotland Twenty-07 study are discussed together, and caution against over-stretching the original reactivity hypothesis. Blood pressure and heart rate were assessed at rest and during an acute mental arithmetic stress task. First, depression, though a putative risk factor for cardiovascular disease, does not appear to confer this risk via exaggerated reactivity, as it was negatively related to reactivity. Second, obesity, another risk factor, was also associated with blunted rather than heightened reactivity. Finally, lower reactivity was related to poorer self-reported health. Similar associations emerged from both cross-sectional and prospective analyses. These seemingly paradoxical results are discussed in terms of implications for the reactivity hypothesis.

Keywords: cardiovascular reactivity, depression, obesity, self-reported health

Introduction

The reactivity hypothesis, as originally conceptualised, proposed that large magnitude cardiovascular reactions to acute psychological stress exposures increase the risk of the development of hypertension (Obrist, 1981). Studies testing the hypothesis have shown that high reactivity is associated with higher blood pressure; the most compelling evidence emerges from prospective studies, where an initial assessment of cardiovascular reactivity is followed by measurement of blood pressure status in the future. For example, in the Twenty-07 study in the West of Scotland, the magnitude of cardiovascular reactions to stress predicted 2-3% of the variance in 5-year upward drift in blood pressure, when controlling for initial resting blood pressure as well as body mass index (Carroll et al., 2003). A number of large scale studies in a range of populations also attest to a reliable positive association between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure status (Carroll et al., 2001; Markovitz et al., 1998; Treiber et al., 1997). The additional risk associated with high cardiovascular reactivity has also been shown to extend to other cardiovascular outcomes including carotid atherosclerosis, carotid intima thickness, and increased left ventricular mass/cardiac hypertrophy (e.g. Everson et al., 1997; Georgiades et al., 1997; Kamarck et al., 1997; Matthews et al., 2006; Treiber et al., 2003).

Recently, high cardiovascular reactivity has also been suggested as a mediator between a wide variety of psychosocial and behavioural risk factors and cardiovascular disease (Chida and Hamer, 2008), such as life events stress (Lepore et al., 1997; Matthews et al., 1997), social support (O'Donovan and Hughes, 2008; Roy et al., 1998), hostility (Suls and Wan, 1993; Vella and Friedman, 2009), and smoking (Davis and Matthews, 1990; Tersman et al., 1991). An obvious corollary of the reactivity hypothesis is that low reactivity during acute stress is an adaptive response and protective against cardiovascular disease. By extension, then, low reactivity would be expected to characterise more positive psychological and behavioural factors implicated in mitigating cardiovascular disease risk. However, it is from research examining aspects of this expanded role for reactivity that a number of seemingly paradoxical findings are beginning to emerge. Analyses from the West of Scotland Twenty-07 study will be used to illustrate that caution is warranted when attempting to stretch the reactivity hypothesis beyond its original postulates. First indications that supposedly negative characteristics or behaviours might not always be associated with higher cardiovascular reactivity emerged from analyses of the associations between life events stress and reactivity in the Twenty-07 study data. For example, socio-economic status was positively associated with acute stress reactivity such that those from manual occupational households had lower cardiovascular responses to acute stress than those from

non-manual households (Carroll et al., 2000). Similarly, given that acute laboratory stress responses are considered to be indicative of how one responds to stressful events in real life, it was expected that those with higher stress ratings for events which had occurred over a two year period, would have greater cardiovascular responses to laboratory stress. However, data from the Twenty-07 study showed that middle-aged and older adults who rated their stressful experiences as more highly disruptive, at the time of occurrence and at the time of recall, exhibited blunted systolic blood pressure reactions to acute mental stress (Carroll et al., 2005). Likewise, among the younger adults in the Twenty-07 study, the total number of events and the number of personal events were negatively associated with systolic blood pressure and heart rate reactions to acute stress, whereas the number of work-related events was negatively associated with diastolic blood pressure and pulse rate reactivity (Phillips et al., 2005b).

The present article will address the scope and the limitations of the reactivity hypothesis through discussion of both cross-sectional and prospective associations between cardiovascular reactivity to acute stress and three key psychosocial/behavioural risk factors; depression, obesity, and self-reported health, in a large community-based sample.

Depression

Depression has been linked prospectively with mortality from cardiovascular disease (Hemingway and Marmot, 1999; Wulsin et al., 1999). The mediators and mechanisms underlying this association have yet to be established, but might include factors such as socio-economic position; ill-health and disability; unhealthy behaviours (Wulsin et al., 1999); increased platelet aggregation (Mikuni et al., 1992); and exaggerated cardiovascular reactions to psychological stress exposure (Kibler and Ma, 2004). With regard to this latter possibility, depression has been associated with a variety of physiological adaptations that suggest altered autonomic function. For example, enhancement of cardiac sympathetic activity relative to vagal tone has been reported in those with depression and subclinical depressive symptoms (Carney et al., 1988; Light et al., 1998), as have increased plasma noradrenalin concentrations in patients with major depression (Rudorfer et al., 1985). Thus, the hypothesis that such autonomic dysregulation in depression may also be manifest as exaggerated cardiovascular reactivity, which in turn increases the risk of cardiovascular pathology, is intuitively appealing. There would appear to be at least some provisional evidence that symptoms of depression may be associated with heightened reactivity. For example, in a study of 91 healthy participants, those with high amounts of depressive symptoms manifested significantly greater systemic vascular resistance in response to a stressor task than did those with low amounts of depressive symptoms

(Matthews et al., 2005). A meta-analysis of 11 relevant studies found small to moderate effect sizes indicative of a positive relationship between depressive symptomatology and cardiovascular reactions to acute psychology stress (Kibler and Ma, 2004). Unfortunately, none of the aggregate effects were statistically significant at conventional levels. Previous studies generally tested fairly small samples and few adjusted for potential confounding variables such as demographic factors and medication status. In contrast, in a larger sample of over 100 coronary artery disease patients, higher depressive symptom scores were associated with lower, not higher, cardiovascular reactions to acute psychological stress, even after controlling for a number of likely confounders (York et al., 2007). The West of Scotland Twenty-07 dataset was used to revisit this issue in a substantial and demographically diverse sample of participants (Carroll et al., 2007). Statistical adjustment for a range of possible confounders was possible. Uniquely, it was also possible to examine prospectively the association between cardiovascular reactivity and symptoms of depression five years later.

Obesity

Obesity is a fast growing epidemic in Western countries (Hughes et al., 2002; WHO, 1997). The adverse health consequences of this increase in adiposity are starting to become apparent. Obesity, defined in terms of a body mass index of 30 kg/m^2 or more, has been consistently linked to all-cause and especially cardiovascular disease mortality (Adams et al., 2006; Allison et al., 1999; Calle et al., 1999; Stevens et al., 1998). It is also associated with a range of cardiovascular and metabolic disease outcomes, such as type 2 diabetes (Ford et al., 1997; Resnick et al., 2000) and hypertension (Hirani et al., 2007; Mokdad et al., 2003), as well as overall cardiovascular disease morbidity (Bogers et al., 2007; Wilson et al., 2002). Abdominal adiposity has also been linked with psychological distress, and it has been argued that an increased vulnerability to stress in the abdominally obese may be manifest as physiological hyper-reactivity (Bjorntorp, 1991). The impact of stress on the neuroendocrine system is thought to promote abdominal fat deposition (Bjorntorp, 1996), and it has been suggested that obesity, and especially central adiposity, will be associated with exaggerated cardiovascular reactions to stress (Davis et al., 1999; Waldstein et al., 1999). The question arises as to whether obesity and exaggerated cardiovascular reactivity to acute stress are positively related or whether they are independent risk factors for cardiovascular pathology. A few mainly small scale studies have attempted to address this issue. Systemic vascular resistance levels during mental stress were negatively correlated with body mass index in 20 young men, but positively associated with waist-hip ratio; no significant associations emerged for blood pressure or cardiac activity during stress (Jern et al., 1992). From a study of 95 adolescents, the peak systolic blood pressure (SBP) reaction to mental stress was larger for participants

in the upper tertile of waist-hip ratios, although neither cardiac nor resistance reactions were associated with abdominal adiposity (Barnes et al., 1998). Waist circumference has been reported to be positively associated with heart rate (HR) and diastolic blood pressure (DBP) reactivity in a sample of 22 older African American men, but these associations did not withstand correction for basal blood pressure and insulin levels (Waldstein et al., 1999). In a contemporary study of 24 women with body mass indices $\geq$ 28 kg/m^2, those with abdominal obesity, i.e. high waist-hip ratios, had higher DBP and systemic resistance reactions, but lower HR reactions, to a speech task (Davis et al., 1999). In the largest study to date, body mass index was not significantly related to cardiovascular reactivity in 225 middle-aged public servants, although waist-hip ratio, a measure of abdominal adiposity, was positively associated with diastolic reactivity; the greater the abdominal adiposity, the higher the reactivity (Steptoe and Wardle, 2005). In addition, it was expected that disturbances in cardiovascular reactivity may reflect autonomic dysfunction which in turn may contribute to the development of obesity and adiposity, yet the upward drift in body mass index and waist-hip ratio over a 3-year follow-up period was not associated with the earlier measures of cardiovascular reactivity (Steptoe and Wardle, 2005). In contrast, greater fatness was related to a blunted vasodilatation response to mental stress in 48 healthy young men (Hamer et al., 2007).

It is difficult to draw firm confident conclusions from the results of these studies, particularly given that most samples were small and poorly representative of the general population, and few adjusted for potential confounding variables, including baseline cardiovascular levels. The most consistent result appears to be a positive association between systemic resistance reactivity, as reflected by DBP and/or total peripheral resistance, and abdominal adiposity, although not all studies report this. The West of Scotland Twenty-07 dataset was again exploited to explore the association between cardiovascular reactivity and adiposity, both cross-sectionally and prospectively (Carroll et al., 2008).

Self-reported health
As well as being considered a health outcome in itself, cardiovascular reactivity has been used to prospectively predict cardiovascular health outcomes (e.g. Everson et al., 1997; Georgiades et al., 1997; Kamarck et al., 1997; Matthews et al., 2006; Treiber et al., 2003). However, the association between cardiovascular reactivity and non-cardiovascular health has attracted little research attention, with the exceptions of depression and obesity, discussed above. However, if reactivity has wider implications for health, it is likely that it might also be associated with self-reported health. Numerous large-scale prospective Epidemiological studies testify that self-reported health predicts various health

outcomes including mortality in a dose-response fashion, independently of traditional risk factors and medical status; those reporting poor health have a mortality risk two to seven times greater than those reporting excellent health (for review, see e.g., (Idler and Benyamini, 1997). If self-reported health is affected by cardiovascular morbidity and its precursory processes, it might be expected to be inversely related to reactivity. It is perhaps curious then that no study has examined whether exaggerated cardiovascular reactions to acute stress are associated with poor self-reported health. Again, the West of Scotland Twenty-07 study was used in analyses examining the relationship between cardiovascular reactions to an acute psychological stress task and self-reported health both cross-sectionally and prospectively (Phillips et al., 2009b).

The present article is a synthesis of the unexpected negative associations between depression, obesity, self-reported health and cardiovascular reactivity to acute stress as conducted as part of the West of Scotland Twenty-07 study. The cross-sectional and prospective associations which emerged from the previous and present analyses are discussed in the light of extensions and interpretations of the reactivity hypothesis.

Method

Participants and Procedure

Each of the studies discussed in this article are based on data derived from the West of Scotland Twenty-07 Study. Participants were all from Glasgow and surrounding areas in Scotland, and have been followed up at regular intervals since the baseline survey in 1987. The study's principle aim was to investigate the processes that produce and maintain socio-demographic differences in health (Benzeval et al., 2009; Macintyre, 1987). Three narrow age cohorts (aged 15, 35, and 55 years at entry) were chosen so that age-specific effects on health could be estimated with greater precision than through using a sample of all ages of the same size. The sample was almost entirely Caucasian reflecting the West of Scotland population from which it was drawn (Ecob, 1987). At the third follow-up in 1995/96, participants were tested during the day in their own homes in a quiet room by specially trained nurses. Given the naturalistic testing setting, participants were usually tested alone, but in 12 percent of cases, a spouse/partner or family member was also silently present, although this variable did not affect the associations presented below. Cardiovascular reactions to a psychological stress task, the paced auditory serial arithmetic test, were measured (Carroll et al., 2000; Carroll et al., 2003), following numerous other assessments of factors such as self-reported health, depressive symptomatology, body mass index, waist and hip circumference, smoking and other unhealthy

behaviours, resting blood pressure, and medication status. Nurses followed a written protocol during every testing session and noted any deviations from protocol, e.g., participant gave up on the test. Such deviations were rare and the data were excluded from the analyses. Reactivity data were available for 1647 participants of whom 592 (36%) were 24-year olds, 624 (38%) were 44-year olds, and 431 (26%) were 63-year olds. The exact mean (SD) ages of the young, middle aged, and eldest cohorts were 23.7 (0.56) 44.1 (0.85), and 63.1 (0.67) years, respectively. There were 890 (54%) women and 757 (46%) men in the sample, with 772 (47%) from manual and 870(53%) from non-manual occupation households. Household occupational group data were not available for five participants. Mean (SD) body mass index, calculated from measured height and weight was 26.7 (4.26) kg/m^2. With the exception of reactivity, all of the above assessments were repeated at the fourth follow-up, 5 years later in 2000/01, at which point data were available for nearly 1300 participants. The mean (SD) temporal lag between the two follow-ups was 5.5 (1.00) years. The study was approved by the appropriate Ethics committees.

Measures

Household occupational group was classified as manual or non-manual from the occupation of the head of household (usually the man) at the third follow-up, using the Registrar General's Classification of Occupations (1980). At both the third and fourth follow-ups, depression was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS is a well-recognised assessment tool that comprises 14 items, seven measuring depression and seven measuring anxiety. The depression subscale emphasises anhedonia and largely excludes somatic items. Further details of the excellent psychometric properties in this scale can be found elsewhere (Carroll et al., 2007). At the third and fourth follow-ups, HADS data were available for 1608 and 1245 participants, respectively.

At both the third and fourth follow-ups, height, using the Leicester Height Measure stadiometer, and weight, using portable electronic scales (Soehnle, Nassau, Germany), were measured and body mass index computed. The standard criterion of $\geq$30 kg/m^2 was used to identify obesity. At the third and fourth follow-ups, BMI data were available for 1647 and 1272 participants, respectively.

To assess self-reported health, participants were presented with the question, 'Would you say that for someone your age your own health is…' and given four response options: excellent, good, fair, poor. The self-reported health data were negatively skewed because only a very small proportion (N = 90 at

the third follow-up and N = 72 at the fourth follow-up) of participants reported poor health, with most (80% and 75%) reporting either fair or good health. Consequently, the excellent and good categories were collapsed, as were the fair and poor categories, to yield a simple binary variable. At the third and fourth follow-ups, an answer to this question was available for 1647 and 1318 participants, respectively.

Participants undertook an acute psychological stress task: the paced auditory serial addition test (PASAT), which has been shown in numerous studies to reliably perturb the cardiovascular system (Ring et al., 2002; Winzer et al., 1999) and to demonstrate good test-retest reliability (Willemsen et al., 1998). Participants were presented with a series of single digit numbers by audiotape and requested to add sequential number pairs while retaining the second of the pair in memory for addition to the next number presented, and so on throughout the series. Answers were given orally and, if participants faltered, they were instructed to recommence with the next number pair. The correctness of answers was recorded as a measure of performance. The first sequence of 30 numbers was presented at a rate of one every four seconds, and the second sequence of 30 at one every two seconds. The whole task took three minutes, two minutes for the slower sequence and one minute for the faster sequence. A brief practice was given to ensure that participants understood the requirements of the task. Only those who registered a score on the PASAT were included in the analyses. Out of a possible score of 60, the mean score was 40.9 (SD = 9.03).

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured by an Omron (model 705CP) sphygmomanometer. This semi-automatic blood pressure device is recommended by the European Society of Hypertension (O'Brien et al., 2001). Following the interview, (at least an hour), there was a formal 5-minute period of relaxed sitting, at the end of which a resting baseline reading of SBP, DBP, and HR was taken. Task instructions were then given, followed by the brief practice. Two further SBP, DBP, and HR readings were taken during the task, the first initiated 20 seconds into the task (during the slower sequence of numbers), and the second initiated 110 seconds later (at the same point during the faster sequence). For all readings, the nurses ensured that the participant's elbow and forearm rested comfortably on a table at heart level. The two task readings were averaged and the resting baseline value subsequently subtracted from the resultant average task value to yield reactivity measures for SBP, DBP, and HR for each participant.

Statistical analysis

Age cohort, sex, and occupational group differences in reactivity and the independent variables were examined using ANOVA and chi-square as appropriate. The main statistic used throughout all of these analyses testing the cross-sectional associations between cardiovascular reactivity and depression, body mass index, and waist-hip ratio was multiple linear regression; reactivity was the dependent variable throughout. After significant findings were observed in models adjusting for only baseline cardiovascular levels, more fully adjusted models were tested in which various likely covariates of reactivity, cohort, sex, household occupational group, performance score on the PASAT, anti-hypertensive medication, were entered before each separate independent variable. Performance score was positively correlated with SBP and HR reactivity, whereas those taking anti-hypertensive medication had lower HR reactivity, throughout, but not to the extent that these relationships attenuated any associations observed, suggesting that the impact of these variables was minimal. For the sake of brevity and comparison, only fully adjusted associations are reported in the present article. Full unadjusted associations can be found in the initial reports of these associations (Carroll et al., 2008; Carroll et al., 2007; Phillips et al., 2009b). The relationships between cardiovascular reactivity and obesity and self-reported health status were tested using analysis of covariance (ANCOVA). Potential confounding variables were entered simultaneously as covariates. Prospective analyses examining the association between reactivity and subsequent depression were by linear regression, and for the associations with subsequent obesity or self-reported health status, by logistic regression. In all prospective linear and logistic regression analyses, models were tested which, in effect, examined the change in the independent variable over time by entering the independent variable at the third follow-up as a covariate, to provide a more stringent test of association.

Results and Discussion

Reactivity

Two-way (baseline × task) repeated measures ANOVAs indicated that the PASAT successfully increased cardiovascular activity overall for SBP, DBP, and HR. There were main effects of cohort and sex on SBP reactivity; reactivity increased with age and men exhibited larger reactions than women. Analogous main effects for cohort and sex were apparent for DBP reactivity. In addition, the effect of occupational status discussed above emerged, such that those from non-manual occupational households exhibited larger DBP reactions. For HR, there were main effects for cohort and occupational status; HR reactivity declined with age and was greater in those from non-manual households. Summary data are presented in Table 1.

Depression and cardiovascular reactivity

The mean depression score was 3.65 (SD = 2.86), but the older two cohorts recorded significantly higher depression scores than the youngest cohort, and women displayed higher scores than men, Finally, those from manual occupational households had higher depression scores than those from non-manual households.   Following adjustment for covariates as described above (baseline cardiovascular level, age cohort, gender, household occupational group, PASAT performance score and antihypertensive medication), and for body mass index, significant negative associations were observed between depression and reactivity: the higher the depression score, the lower the reactivity, for both SBP and HR. As 71 (4%) of the sample reported taking reported taking antidepressants, this variable was additionally adjusted for, but the negative associations between depressive symptomatology and cardiovascular reactivity were not attenuated. The fully adjusted associations between depressive symptom score, using the cut-off of ≥ 8 to indicate possible caseness, and SBP and HR reactivity are displayed in Figure 1 as an illustration of the nature of these associations.

Recently, a novel prospective analysis was run in which depression score at follow-up 4 was entered as the dependent variable and depression score at follow-up 3 as a covariate. This enabled examination of the associations between reactivity and change in depression score over time. In these analyses, neither SBP nor DBP reactivity were related to HADS depression score five years later. However, HR reactivity was again negatively associated with depression symptomatology, such that those with lower reactivity were more likely to display an increased depression score at the fourth follow-up.

In these data, higher depressive symptom scores were associated with lower HR reactivity. What is especially compelling about these negative associations is that they were still evident following adjustment for a relatively comprehensive range of covariates. A similar study examined the depression and reactivity association in over 100 coronary artery disease patients (York et al., 2007). They measured symptoms of depression and reactivity during a public speaking stress task. Again, higher depressive symptom scores were associated with lower, not higher, reactivity. Thus, it would appear that as putative risk factors for cardiovascular pathology, high levels of depressive symptomatology and exaggerated cardiovascular reactions to stress may operate independently of one another. More recently, it has also been shown that individuals with sub-clinical depression levels displayed blunted cardiovascular responses to tasks associated with the consequences of punishment and reward in comparison to those with higher depression scores (Brinkmann et al., 2009). Similarly, depression is also characterised by diminished emotional responsiveness to pleasant stimuli and reward

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(Bylsma et al., 2008). For example, in a recent study depressed patients exhibited blunted emotional reactions to anticipated reward relative to controls, but did not differ from controls in their emotional responsiveness to anticipated punishment (McFarland and Klein, 2009). This also begs the question, answerable only by prospective designs, of whether low reactivity could be a risk marker for depression, and in the present article we present novel preliminary evidence that this is the case; lower HR reactivity was significantly related to an increase in depressive symptoms over the subsequent five years.

Body mass index, obesity, and cardiovascular reactivity

At the earlier follow-up the younger cohort had lower body mass indices than the other two cohorts. Body mass index did not differ significantly between the sexes or between occupational class groups. Two hundred and twenty five (14%) of the participants met the criterion for obesity; proportionally fewer of the younger cohort were identified as obese. The frequency of obesity did not vary significantly by sex or occupational class, but participants who were taking blood pressure lowering medication (9%) had greater body mass indices than those not taking medication. Current smokers had significantly lower body mass indices than ex- or never smokers. Consequently, smoking was added to the range of covariates in analyses of reactivity and obesity. In the fully-adjusted analyses, there was a significant negative association between body mass index and HR reactivity. Obese participants also exhibited much smaller HR reactions to stress than their non-obese counterparts. Finally, given the associations with depression described above, we have since adjusted for depression status as well as the previous covariates, and the associations described above remained highly statistically significant. The fully adjusted association between obesity and HR reactivity is shown in Figure 1 as an illustration of the nature of the relationship.

As might be expected, body mass index significantly increased across the five years between follow-ups, and at the later follow-up, a higher proportion, 261 (21%), of participants met the criterion for obesity. Reactivity did not predict the rise in either body mass index in the five years between the third and fourth follow-ups. However, in fully adjusted analyses with obesity at the fourth follow-up as the dependent variable and obesity at the third follow-up as a covariate, lower HR reactivity was associated with an increased risk of becoming obese over the five years between follow-ups.

The cross-sectional and prospective analyses of the associations among reactivity and body mass index and obesity show that, contrary to expectations based on the indicative rather than definitive outcomes

of the few previous small scale studies, low cardiac reactivity was associated with a greater body mass index and greater likelihood of being obese. In addition, in prospective analyses low cardiac reactivity was associated with an increased risk of becoming obese in the subsequent five years. Again, these outcomes withstood adjustment for a range of socio-demographic factors and medication status. There is some other evidence that whereas the obese have elevated sympathetic tone in the resting state (Tentolouris et al., 2006), their sympathetic nervous system may be less responsive to stimulation. For example, after ingestion of a meal, there is a postprandial sympathetic nervous system response as reflected by higher plasma norepinephrine concentrations and an increased low- to high-frequency ratio in the heart rate variability spectrum (Tentolouris et al., 2003; Welle et al., 1981). However, this effect has been observed to be much smaller in obese as opposed to lean individuals (Tentolouris et al., 2003). Further, the present findings do not appear to be driven by higher resting cardiovascular levels among obese individuals resulting in a ceiling effect on reactivity, given that these associations remained significant following adjustment for baseline cardiovascular levels. Additional support can be found in the observation that changes in heart rate and muscle sympathetic nerve stimulation after the infusion of antihypertensive and antihypotensive drugs were found to be significantly smaller in the obese than the non-obese (Grassi et al., 1995). Further, obesity is associated with a state of leptin resistance in humans, and hyperleptinaemia is related to lower sympathetic nervous system activity in obese individuals (Quilliot et al., 2008), whereas circulating leptin has been shown to relate to acute stress-induced increases in heart rate in non-obese humans (Brydon et al., 2008). Thus, it is possible that obese individuals become resistant to the sympatho-activating effects of leptin, resulting in blunted reactivity.   In sum, the finding that it is low cardiac reactivity that characterises obesity would appear to be credible. Indeed, low reactivity, possibly by reflecting generally blunted sympathetic nervous system response to acute challenge, may even be a risk marker for developing obesity.

Self-reported health and cardiovascular reactivity
Overall, 1211 (74%) and 967 (73%) of the participants reported that they enjoyed relatively good or excellent health at the third and fourth follow-ups respectively. For 134 (10%) of the sample, their self-reported health improved between follow-ups, whereas for 176 (13%) it deteriorated. At the third follow-up, proportionally more of those from manual (30%) compared to non-manual occupational households (23%) reported poor or only fair health. This difference between manual and non-manual occupational groups was preserved at the fourth follow-up. There were no sex differences in self-reported health at either follow-up and significant variation with age emerged only at the third follow-up, where, compared to the other two cohorts (30%), proportionally fewer of the middle cohort (20%)

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reported relatively poor or only fair health. Given the associations reported above, depression score and body mass index were also added to the growing list of covariates. Participants who reported relatively excellent or good health at the third follow-up had larger SBP and DBP reactions than those who reported poor or only fair health. The fully adjusted associations are displayed in Figure 1 as an illustration of the extent of the associations.

In logistic regression analyses, with full adjustment, in which self-reported health status at the third follow-up was also entered as a covariate, cardiovascular reactivity predicted the change in health status five years later for DBP and HR reactivity, and for SBP reactivity, although the latter was a non-significant trend. These positive associations indicate that participants with exhibiting relatively higher cardiovascular reactivity had better self-reported health five years later, independent of their earlier self-reported health.

The relationships between cardiovascular reactivity and self-reported health both cross-sectionally and prospectively, as before, withstood adjustment for a range of possible confounders, including body mass index, depressive symptomatology, and baseline cardiovascular levels. Thus, as with depression and obesity, it was low reactivity that was associated with the poorer health outcomes. We have recently been made aware of supporting data. In a cross-sectional study of 725 Dutch men and women aged between 55 and 60 years, those with large cardiovascular reactions to acute psychological stress reported better health than those with small reactions; the same held true for cortisol reactivity (de Rooij and Roseboom, in press). Thus, it would seem that it is blunted reactivity that was related to poor self-reported health and, in the case of our analysis, presaged a relative deterioration in subjective health over time. Self-reported health is likely to be a function of numerous factors and to depend on the integrity of multiple biological systems, not simply the subjective impact of occult or manifest cardiovascular disease. One system that would appear to be critical in this context is the immune system. What is called the acute stress-induced immuno-enhancement hypothesis proposes that acute stress up-regulates various aspects of immunity and that this has functional implications for host defence such that exposure to acute stress, and by implication large magnitude stress reactions, might actually enhance the immune system's ability to respond to a contemporary antigen challenge (Dhabhar, 2002; Edwards et al., 2007). However, a full discussion of this issue is beyond the scope of the present review.

Concluding remarks

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There are a few factors to address when considering the consensus regarding blunted or lower reactivity emerging from this synthesis of analyses from the West of Scotland Twenty-07 study. First, and naturally, the consensus of findings should be treated with caution, given that they are emerging from the same dataset. However, the Study's principle aim was to investigate the processes that generate and maintain socio-demographic differences in health (Macintyre, 1987), thus participants were chosen randomly with probability proportional to the overall population of the same age within a zip code area (Ecob, 1987). This careful match between the sample and general population makes us confident about our ability to generalise to the population at large. Further, the number of potential confounders our results withstood adjustment for, and the more recent emergence of some replicative and supportive data, discussed above, suggests that these findings are trustworthy, robust, replicable, and not simply a phenomenon of this particular study. Second, the effect sizes for the results presented above were small by conventional standards. This, though, was our *a priori* expectation based on previous research and reinforces the value of large samples when examining some of the more subtle correlates of cardiovascular reactivity. Our effects are also of the same order as the positive associations between cardiovascular reactivity and future blood pressure status in this sample (Carroll et al., 2003) and others (e.g. Carroll et al., 1995; Carroll et al., 2001; Markovitz et al., 1998). In addition, these effect sizes in the categorical analyses are similar to, for example, those linking BMI, as a categorical variable, and future coronary heart disease risk (see e.g., Bogers et al., 2007), which is considered to be a clinically significant association. Third, performance on the stress task was adopted as a measure of task engagement. Although this seems reasonable, in retrospect it might have proven useful to have included self-report measures of stress task impact. Nevertheless, performance score correlated with reactivity in the expected direction. Finally, only blood pressure and HR were measured. Although, it would have been useful to have a more comprehensive assessment of haemodynamics of the sort afforded by impedance cardiography, the large sample and the decision to test participants in their homes precluded this. In this context, it is worth noting that most previous studies of this magnitude have similarly restricted their focus to blood pressure and heart rate.

It would appear that hypertension and other cardiovascular disease manifestations aside, high cardiovascular reactivity may not always be associated with negative health outcomes and behaviours. The present research presents preliminary evidence that low reactivity may characterise those with more symptoms of depression, those who are fatter, and those with worse self-reported health. Whereas the cardiovascular health consequences of excessive cardiovascular reactivity constitute a coherent whole, it is difficult to see what unites these apparently diverse corollaries of blunted

reactivity. Leaving aside self-reported health, as its determinants have yet to be subjected to concerted study, depression and obesity are both characterised, to an extent, by behavioural expressions of disordered motivation towards food in obese individuals (Stice et al., 2008), and toward pleasant stimuli (Bylsma et al., 2008) and reward (McFarland and Klein, 2009) among those with depression. It is possible that blunted reactivity may be a physiological marker of such motivational dysregulation. The neural correlates and mechanisms of such processes are discussed in more depth elsewhere in this special issue by Lovallo and colleagues.

In a recent meta-analysis, other negative psychological or behavioural traits, including anxiety, neuroticism, and negative affectivity, were also revealed to be related to decreased cardiovascular reactivity (Chida & Hamer, 2008). Although the mechanisms of such associations are not yet fully understood, the growing literature associated with low cardiovascular reactivity suggests that we need a new perspective on reactivity and an expanded conceptual model of how departures from normal physiological response patterns have implications for adverse health outcomes. Blunted, as well as exaggerated, reactivity may be non-adaptive and bad for our health.

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Table 1. Mean (SD) SBP, DBP, and HR reactions for the whole sample and by cohort, sex, and occupational status.

	SBP		DBP		HR	
	Baseline	*Reactivity*	*Baseline*	*Reactivity*	*Baseline*	*Reactivity*
Whole sample	129.1	11.6	78.9	7.0	66.7	8.2
	(20.50)	(11.72)	(11.60)	(8.61)	(10.80)	(9.82)
Age Cohort:						
Youngest	120.0	10.2	73.4	6.8	67.6	10.0
	(14.99)	(10.05)	(10.10)	(8.98)	(11.06)	(10.60)
Middle	127.2	12.2	80.7	7.1	66.6	7.8
	(18.13)	(11.41)	(11.17)	(8.06)	(11.08)	(10.04)
Eldest	144.4	12.4	83.8	7.0	65.7 (9.97)	6.0
	(21.66)	(13.92)	(11.16)	(8.91)		(7.73)
Sex:						
Male	134.9	12.9	81.4	7.1	64.7	8.8
	(18.27)	(11.72)	(11.12)	(8.40)	(10.43)	(9.83)
Female	124.3	10.4	76.8	6.8	68.4	7.6
	(21.05)	(11.61)	(11.61)	(8.79)	(10.83)	(9.80)
Occupational group:						
Manual	130.5	11.3	79.4	6.6	66.9	7.0
	(21.40)	(12.13)	(11.93)	(9.02)	(11.23)	(9.56)
Non-manual	127.9	11.7	78.5	7.3	66.5	9.2
	(19.65)	(11.35)	(11.31)	(8.23)	(10.43)	(9.94)

Figure 1. Cross-sectional fully adjusted associations between cardiovascular reactivity and depression score, obesity status, and self-reported health.