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# Blunted cardiovascular reactivity to psychological stress and prospective health: a systematic review

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## ABSTRACT

Novel research demonstrates that lower or 'blunted' cardiovascular reactions to stress are associated with a range of adverse outcomes. The aim of the current review was (1) to examine the prospective outcomes predicted by blunted cardiovascular reactivity and (2) to identify a range of blunted cardiovascular reaction levels that predict these outcomes. Electronic databases were systematically searched (Medline, PsycArticles, PsycInfo, CINAHL, PubMed, Web of Science). Studies were included if they examined the prospective influence of blunted cardiovascular reactivity to psychological stress (SBP, DBP or HR) on a negative health, behavioural or psychological outcome. A total of 23 studies were included in the review. Blunted reactivity predicted (1) adverse cardiovascular health, primarily in cardiac samples (e.g., myocardial infarction, carotid atherosclerosis) and (2) outcomes associated with motivational and behavioural dysregulation in healthy samples (e.g., obesity, smoking addiction, depression). The cardiovascular reactivity threshold levels that were predictive of adverse health outcomes ranged between  $-3.00$ – $12.59$  bpm (14.41% to 136.59% lower than the sample mean) and  $-2.4$ – $5.00$  mmhg (65.99% to 133.80% lower than sample mean), for HR and DBP respectively. We posit that blunted reactions lower than, or equal to, the ranges reported here may be utilised by clinicians and researchers to identify individuals who are at increased risk of adverse cardiovascular health outcomes, as well as outcomes associated with motivational and behavioural dysregulation.

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Psychological stress;  
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cardiovascular disease;  
prospective health; blunted  
reactivity

## Introduction

A primary focal point of psychosomatic research has examined the role of psychological stress in the pathogenesis of the cardiovascular disease. Corroborated by over 40 years of research, the cardiovascular reactivity hypothesis has been situated at the forefront of the stress and cardiovascular health literature. As originally conceptualised, this hypothesis propounds that persistently exaggerated or prolonged cardiovascular responses to psychological stress promotes the development of cardiovascular disease (Obrist, 1981). Claims posited by the original reactivity hypothesis have been substantiated by an array of prospective studies, whereby exaggerated cardiovascular reactions to stress predict future hypertension (Carroll et al., 1995; Carroll et al., 2001; Carroll et al., 2003; Carroll, Ginty, Painter, et al., 2012; Markovitz et al., 1998; Treiber et al., 1997), atherosclerosis (Barnett et al., 1997; Matthews et al., 1998), increased left ventricular mass/left-ventricular hypertrophy (Georgiades et al., 1997; Kapuku et al., 1999), and cardiovascular disease mortality (Carroll, Ginty, Der, et al., 2012).

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Additional support for this hypothesis comes from the rather coherent pathophysiological mechanisms that directly facilitate the association between exaggerated cardiovascular reactivity to psychological stress and adverse cardiovascular health. In brief, these include: (1) the direct triggering of acute cardiovascular events (Tofler et al., 1990); (2) acute stress-induced damage to the endothelium of the arterial intima due to mechanical (hemodynamic) or chemical (epinephrine, norepinephrine) forces, which then initiates the process of atherosclerosis and the subsequent formation of atheromatous plaques (Krantz & Manuck, 1984); (3) increased stress-induced myocardial ischemia due to vasoconstriction (Goldberg et al., 1996) which may deprive the heart of oxygenated blood and precipitate negative cardiac events (Jiang et al., 1996); (4) acute stress-induced cardiac arrhythmia including ventricular fibrillation and bradyarrhythmias which may result in a sustained loss of blood flow and sudden cardiac death (Kamarck & Jennings, 1991); and (5) acute stress-induced changes to blood viscosity due to hemoconcentration, rendering venerable arteriosclerotic plaques at increased risk of fissuring, subsequently engendering the formation of a thrombus (Veldhuijzen Van Zanten et al., 2004; Zraggen et al., 2005).

Given the particular research emphasis placed on the pathogenic effect of exaggerated reactivity to psychological stress on health, low (or blunted) cardiovascular reactivity has, by implication, previously been assumed benign, or protective. However, recent evidence suggests that blunted cardiovascular reactivity is associated with a range of outcomes that may reflect deficits in motivational and behavioural dysregulation, including depression, obesity, alcohol addiction, and smoking (Carroll et al., 2009; Carroll et al., 2017; Phillips, 2011; Phillips et al., 2013). Variations in cardiovascular reactivity to acute psychological stress are posited to reflect altered functioning at one of three levels; the limbic system and prefrontal cortex (level 1), the hypothalamus and brain stem (level 2) or at the peripheral tissues (level 3) (Lovallo, 2011; Lovallo & Gerin, 2003). Blunted cardiovascular reactions are suggested to reflect sub-optimal functioning of the fronto-limbic system (level 1), resulting in motivational and behavioural dysregulation (Carroll et al., 2017; Gianaros et al., 2005; Ginty et al., 2013). Furthermore, given that many of the cardiovascular risk factors associated with blunted reactivity (e.g., depression, obesity, and smoking addiction) may reflect deficits in motivation or behavioural control, the heretofore-assumed protective effect of blunted reactivity for cardiovascular health is questionable. Indeed, prospective studies have begun to identify that blunted cardiovascular reactivity to psychological stress predicts cardiovascular disease outcomes in samples with pre-existing cardiovascular disease (Kupper et al., 2015).

Furthermore, there may be important differences between the outcomes of blunted cardiovascular reactivity to stress in healthy samples compared to diseased samples. To date, the literature has not clearly delineated what blunted cardiovascular reactivity to stress means when observed in clinical samples, nor whether this reflects the same processes and outcomes in healthy samples. Additionally, a precise or predictive value of blunted cardiovascular reactivity for prospective health has yet to be quantified. Without a designated threshold, researchers are left to arbitrarily determine if responses are blunted and signal poor health, or rather, are simply normative (lower) responses to psychological stress. In the absence of clinically relevant ranges of blunted cardiovascular reactivity, much of the cardiovascular reactivity research on healthy populations, designed to identify where psychosocial factors are important moderators, is limited by the fact researchers have been left without any clear guidance to decide if the observed lower responses to the stressor are good, bad, or benign. This has greatly limited the field, restricting the clinical application and relevance of such research findings. While a recent review conducted by Turner et al. (2020) summarised the prospective outcomes predicted by physiological reactivity to acute psychological stress, they did not report a threshold of reactivity that was predictive of prospective outcomes, and limited their focus on healthy samples that were free from cardiovascular disease.

In order to advance the field and extend on the findings of Turner et al. (2020), we undertook a systematic literature review of prospective studies to identify clinically relevant thresholds of blunted cardiovascular reactivity to stress in both healthy and cardiac samples. The review has two key aims: firstly, we aim to summarise the prospective outcomes predicted by blunted cardiovascular reactivity

to psychological stress. Here, we will review findings in the literature pertaining to blunted cardiovascular reactivity and prospective health outcomes. We expect that blunted cardiovascular reactivity to stress will predict (1) a range of adverse cardiovascular health outcomes, primarily amongst cardiac patients, and (2) a range of outcomes that reflect deficits in motivation and behavioural regulation. Secondly, we aim to quantify what precisely constitutes a clinically relevant blunted response for heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) that prospectively confers an increased risk of adverse health, behavioural and psychological outcomes. Finally, unlike the Turner et al. (2020) review, we included studies that employed a follow-up period of  $\leq 1$  year to examine the influence of blunted reactivity on more recent outcomes, and limited our focus to blunted cardiovascular parameters (SBP, DBP and HR) that are most notably known to predict poorer physical and psychological health outcomes (Carroll et al., 2017).

## Methods

### *Search strategy*

The current systematic review was undertaken in accordance with the recommended guidelines reported in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al., 2009). Additionally, this systematic review was also pre-registered on PROSPERO CRD42018090719. In July 2020, the following databases were searched; Medline, PsycArticles, PsycInfo, CINAHL, PubMed and Web of Science. The search terms included (cardiovascular OR cardiac OR physiological OR 'heart rate' OR 'blood pressure') And reactivity And stress And (prospective OR longitudinal OR follow-up). Furthermore, in order to maximise the number of retrieved articles, no limiters or filters were used when searching databases.

A follow-up search was conducted prior to publication in February 2022. All initial databases were searched using the original search string. Databases were searched from 2020 to date.

### *Inclusion criteria*

Studies were included in the current review if: (1) the manuscript was a peer-reviewed article in English; (2) employed human samples; (3) examined cardiovascular reactivity to acute psychological stress using a laboratory stressor (excluding reviews); (4) reported either SBP, DBP, or HR reactivity; (5) employed a prospective/longitudinal design, whereby a blunted/lower cardiovascular response predicted a negative outcome (negative health or behaviour) at the follow-up; (6) was free from the administration of pharmacological agents.

We defined negative health or behavioural outcomes as (1) any outcome that represents poor physical (e.g., hypertension) or mental health (e.g., depression), or (2) any behavioural/cognitive factors that are known to influence health (e.g., poor perseverance).

Given that the primary aim of the current study was to synthesise findings pertaining to blunted cardiovascular reactivity and prospective health, studies reporting findings of exaggerated cardiovascular reactivity were excluded from the review.

### *Screening and data management*

Articles were downloaded from each database separately and were imported into Endnote (EndNote X9). Following the removal of duplicates, all remaining titles and abstracts were screened in order to remove articles that did not meet the inclusionary criteria. Subsequently, the full text of the remaining articles were screened in order to identify studies that would be included in the final review. All screening was initially conducted by the first author (AOR). In order to ensure that the screening process was thorough, a 20% random sample of retrieved articles was independently reviewed by the third author (SG). There were no disagreements regarding the inclusion/exclusion of articles.

Data from each study included: (1) the authors' names; (2) the year of publication; (3) the study population/study cohort; (4) age and sex of the sample at baseline; (5) the type of psychological stress task employed; (6) the length of the follow-up; (7) the negative health/behavioural outcomes assessed; (8) the significant findings of blunted reactivity; (9) the blunted cardiovascular response that was exhibited (if reported); and (10) how the blunted response was computed. Data was manually extracted by the first author (AOR).

Study quality and risk of bias was assessed using a modified version of the Cochrane Tool to Assess Risk of Bias (Cochrane Collaboration, ). This adapted version was replicated from a recent similar systematic review on cardiovascular reactivity (Turner et al., 2020). The quality assessment questionnaire consisted of five main items including: (1) Can we be confident in the assessment of exposure? (2) Can we be confident in the assessment of outcome? (3) Can we be confident that the outcome of interest was not present at the start of the study? (4) Can we be confident in the assessment of the presence or absence of relevant confounders? (5) Was the follow-up of cohorts adequate? Each of the items was scored as either 'Definitely yes', 'Probably yes', 'Probably no' or 'Definitely no'. These scores were transformed to numerical values between 1 and 4, with higher numbers indicating greater study quality and lower risk of bias.

Unadjusted, partially adjusted and fully adjusted significant findings (when available), were extracted in order to determine if effects remained significant following the adjustment of relevant confounding variables. Additionally, giving the variation in statistical techniques employed across studies, as well as differences in the operationalisation of reactivity variables as categorical or continuous constructs, a blunted response (if reported) was extracted using two different methods. Firstly, when a continuous independent variable (continuous cardiovascular reactivity score) predicted a categorical outcome (e.g., obese vs. non-obese), the mean cardiovascular response of the negative health/behaviour group (e.g., obese group) was extracted. Secondly, when a categorical independent variable (e.g., upper vs lower quartile of cardiovascular reactivity) predicted a continuous or categorical outcome (e.g., greater BMI), the mean response of the lower category of the independent variable was considered blunted. This allowed for the successful extraction of a blunted response in line with the significant statistical analyses employed across studies. Mean blunted responses could not be extracted from studies employing correlational designs (dimensional independent and dependant variables), as no group or category was reported as blunted (e.g., obese, depressed etc.).

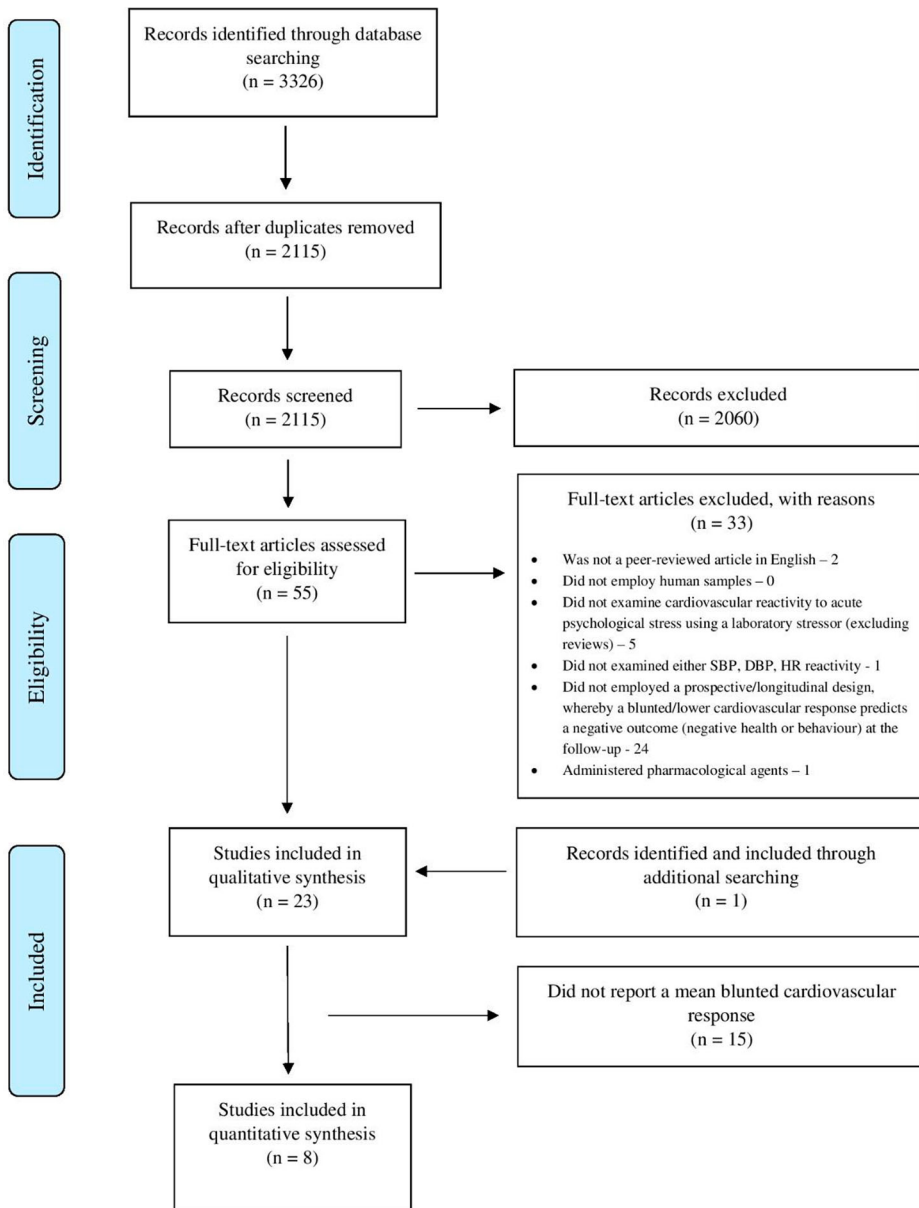
Additionally, given that cardiovascular reactivity has been shown to vary across studies due to sample characteristics (e.g., age and sex) and differential stress tasks (Brindle et al., 2014), we also computed a percentage change score of blunted reactivity in relation to the sample mean. If the sample mean was not directly available, it was calculated based on a subsample-weighted mean.

## Results

### *Results of search and study characteristics*

A total of 3326 articles were retrieved across all databases. After the removal of duplicates ( $n = 1211$ ), the title and abstract of 2115 articles were screened. During the screening of titles and abstracts, 2060 articles were excluded. The full text of the remaining 55 articles were screened and a total of 22 studies were identified to be included in the review. An additional search was completed prior to publication (February 2022) and 452 articles were identified. After the removal of duplicates ( $n = 137$ ), a total of 315 articles remained to be screened. During the screening of titles and abstracts, 309 articles were removed. The full text of 6 articles were screened and 1 eligible article was identified. Thus, 23 articles were included in the review (see [Figure 1](#)).

There was 14,630 participants across the 23 included studies. The mean sample age of participants across studies at baseline ranged from 13.90 to 66.60 years. Many studies used data from large cohort studies including the Dutch Famine Birth Cohort Study (2 studies), the West of Scotland twenty-07 study (5 studies), and the Coronary Artery Risk Development in Young Adults Study



**Figure 1.** PRISMA flow diagram of article identification and screening.

(2 studies). Follow-up periods ranged from 4 weeks to 23 years across included studies. Common psychological stressors included mental arithmetic, speech, video game, stroop, mirror tracing and negative event recall/imagery tasks.

### **Assessment of quality/bias**

Scores for risk of bias and quality assessment are reported in [Table 1](#). Each study was scored on five items of risk of bias and quality assessment. As per previous reviews (Turner et al., 2020), each item was scored on a 4-point scale (1 = Definitely no, 2 = Probably no, 3 = Probably yes, 4 = Definitely yes). A total score for each study was computed as the sum of these four items. For item 1 (Can we be

**Table 1.** Risk of bias and quality assessment.

	Q1. Can we be confident in the assessment of exposure?	Q2. Can we be confident in the assessment of outcome?	Q3. Can we be confident that the outcome of interest was not present at the start of the study?	Q4. Can we be confident in the assessment of the presence or absence of relevant confounders?	Q5. Can we be confident that the follow-up of cohorts was adequate?	Total score
	Was an adequate acclimatisation period included the cardiovascular reactivity protocol? Was a true resting baseline assessed? Did the stress tasks significantly perturb the cardiovascular system?	Was the most appropriate measure used to assess the particular outcome of focus?	Was there evidence that the outcome was not present at time 1/baseline? For cardiovascular outcome, were patients healthy (free from cardiac conditions) at baseline? Did the study examine change scores from time 1/ baseline to the follow-up and/or controlled for scores on the outcome measure that was assessed at time 1/baseline in the prospective analyses?	Did the study include relevant confound variables that are associated with cardiovascular reactivity and the particular outcome of focus?	Was there evidence that missing data at the follow-up was not associated with either cardiovascular reactivity or scores on the outcome measure or markers of the outcome measure (e.g., disease severity for mortality or cardiac events)?	
Ahern et al. (1990)	2	2	3	4	2	13
al'Absi et al. (2005)	3	4	4	4	4	19
Brindle et al. (2016)	4	3	4	4	3	18
Brody and Rau (1994)	3	4	4	4	2	17
Carroll et al. (2008)	4	4	4	4	2	18
De Vries-Bouw et al. (2011)	4	4	4	1	4	17
Ginty et al. (2015)	4	4	4	4	4	20
Ginty et al. (2011)	4	4	4	4	2	18
Ginty et al. (2021)	4	4	3	3	2	16
Halligan et al. (2006)	4	4	4	2	3	17
Heponiemi et al. (2007)	2	4	1	3	2	12
Herd et al. (2003)	3	4	3	4	4	18
Kupper et al. (2015)	3	4	3	4	4	18
Lawler and Schmied (1992)	3	3	4	2	2	14
Matthews et al. (2006)	2	4	2	3	1	12
Phillips et al. (2009)	4	3	4	4	2	17
Phillips, Der, et al. (2011)	4	3	4	4	2	17
Phillips, Hunt, et al. (2011)	4	3	4	4	2	17

(Continued)

**Table 1.** Continued.

	Q1. Can we be confident in the assessment of exposure?	Q2. Can we be confident in the assessment of outcome?	Q3. Can we be confident that the outcome of interest was not present at the start of the study?	Q4. Can we be confident in the assessment of the presence or absence of relevant confounders?	Q5. Can we be confident that the follow-up of cohorts was adequate?	Total score
Phillips et al. (2012)	4	3	4	4	2	17
Sherwood et al. (2017)	3	4	3	4	4	18
Wangelin and Tuerk (2015)	2	4	4	1	2	13
Yano et al. (2016)	3	4	1	3	2	13
Yuenyongchaiwat and Sheffield (2017)	4	3	4	4	2	17

Notes: Higher scores indicate a lower risk of bias and greater study quality. Scores on subscales can range from 1 to 4. Total scores can range from 5 to 20.

confident in the assessment of exposure?), 19 (82.61%) studies were scored as either 'definitely yes' or 'probably yes' and four (17.39%) studies scored 'probably no'. For item 2 (Can we be confident in the assessment of outcome?), 22 (95.65%) were scored as 'definitely yes' or 'probably yes', with only one (4.35%) study scored as 'probably no'. For item 3 (Can we be confident that the outcome of interest was not present at the start of the study?), 20 (86.96%) studies were scored as 'definitely yes' or 'probably yes', with three (13.04%) studies scored as 'probably no' or 'definitely no'. For item 4 (Can we be confident in the assessment of the presence or absence of relevant confounders), 19 (82.61%) of the included studies were scored as either 'definitely yes' or 'probably yes'. Two (8.70%) studies were scored as 'probably no' and the remaining two (8.70%) studies were scored as 'definitely no'. For the final item (can we be confident that the follow-up of cohorts was adequate?), 8 (34.78%) studies were scored as 'definitely yes' or 'probably yes'. Fourteen (60.87%) studies were scored as 'probably no' and one (4.35%) study was scored as 'definitely no'.

The overall average scores across studies were 3.35, 3.61, 3.44, 3.39 and 2.57 for items 1–5 respectively, indicating a generally low risk of bias and a good quality across each item individually. The total risk of bias/quality assessment scores ranged between 12 and 20 with a mean 16.35, indicating that overall, the included studies had a low risk of bias and were of good quality.

### Synthesis of results

Of the 23 studies examining blunted reactivity to acute psychological stress on prospective outcomes, 8 found that blunted reactivity predicted adverse cardiovascular health outcomes, while 15 studies found blunted cardiovascular reactivity to predict outcomes associated with motivational and behavioural dysregulation. For cardiovascular outcomes, 4 studies reported a significant effect in cardiac samples and 4 four studies reported effects in healthy samples. Heart rate reactivity was the most common cardiovascular parameter associated with negative outcomes at the follow-up period (18 studies, 78.26%), while 6 (26.09%) studies reported a significant effect of SBP reactivity, and 6 (26.09%) studies reported an effect of DBP reactivity (see Table 2).

Across all health, behavioural and psychological outcomes, a mean blunted response could be extracted for six studies for HR reactivity, one study for SBP reactivity, and three studies for DBP reactivity. For HR reactivity, the mean blunted response ranged between  $-3.00$  and  $12.59$  bpm across studies. For DBP reactivity, the mean blunted response ranged from  $-2.40$  to  $5.00$  mmHg. A lack of mean blunted responses reported for SBP across studies precluded the computation of ranges for this cardiovascular parameter.

Mean blunted cardiovascular responses that predicted adverse health, behavioural and psychological outcomes ranged between 14.41% and 136.59% lower than the sample mean for HR reactivity, and between 65.99% and 133.80% less than the sample mean for DBP reactivity.

### **Adverse cardiovascular health**

#### **Healthy samples**

In healthy populations, blunted HR reactivity predicted a greater increase in resting DBP (Brody & Rau, 1994), greater intima-media thickness of the carotid artery/carotid atherosclerosis (Heponiemi et al., 2007), and coronary artery calcification (Matthews et al., 2006), at the follow-up period. Furthermore, a multivariate analyses conducted by Brindle et al. (2016),<sup>1</sup> revealed that in comparison to a cluster of exaggerated reactors (exaggerated SBP, DBP and HR reactivity), a cluster characterised by *equally* exaggerated SBP and DBP, but lower HR reactivity, was at increased risk of hypertension diagnosis; these clusters only differed on their HR response. None of the studies reported an effect of either blunted SBP or DBP on prospective cardiovascular health in healthy samples; however, Matthews et al. (2006) also reported that those with exaggerated SBP reactivity had greater coronary artery calcification at follow-up.

#### **Cardiac samples**

In cardiac populations, blunted HR reactivity predicted death or cardiac arrest amongst myocardial infarction patients (Ahern et al., 1990), while blunted DBP predicted mortality in heart failure patients (Kupper et al., 2015). In patients post-coronary artery bypass graft surgery, blunted HR and DBP reactivity predicted clinical events (angina pectoris, myocardial infarction, cerebrovascular accident or death) (Herd et al., 2003). Finally, blunted SBP and DBP reactivity predicted cardiac hospitalisation or death in heart failure patients (Sherwood et al., 2017).

#### **Threshold of blunted cardiovascular reactivity for cardiovascular outcomes**

Six studies (75%) reported a significant effect of blunted HR reactivity on adverse cardiovascular outcomes. While three (37.5%) studies reported an effect of DBP reactivity, only one (12.5%) study reported an effect of SBP reactivity on adverse cardiovascular outcomes.

Of the 8 studies reporting an effect of blunted reactivity to stress on adverse cardiovascular outcomes, a mean blunted response could be extracted for four studies (see Table 3). A cardiovascular response equal to, or lower than values on HR reactivity between 4.00 and 4.40 bpm, and on DBP reactivity between -2.40 and 5.00 mmHg on DBP reactivity appears to predict adverse cardiovascular outcomes. A lack of mean blunted responses reported for SBP across studies precluded the computation of ranges for these cardiovascular parameters.

Only one study reported a mean blunted response to predict adverse cardiovascular outcomes in a healthy population (4.40 bpm) (Matthews et al., 2006). This HR response was of similar magnitude to the mean blunted HR response that predicted adverse cardiovascular health in cardiac patients (4.00 bpm) (Ahern et al., 1990), indicating that similar levels of reactivity predict poorer cardiovascular outcomes in both healthy and diseased populations.

The mean blunted cardiovascular response that predicted adverse cardiovascular health outcomes ranged between 18.52% and 45.28% lower than the sample mean for HR reactivity, and between 65.99% and 133.80% less than the sample mean for DBP reactivity.

#### **Non-cardiovascular outcomes (health, behavioural, and cognitive)**

A total of 15 studies found blunted cardiovascular reactivity to stress to predict other non-cardiovascular related outcomes; those proposed to be reflective of motivational or behavioural dysregulation. Blunted HR reactivity predicted an increased likelihood of becoming obese (Carroll et al., 2008; Phillips et al., 2012), lower perseverance (failure to complete a follow-up study) (Ginty et al.,

**Table 2.** Study characterises, findings and thresholds of blunted reactivity.

Authors/Year	Sample size for prospective analyses	Study population or name of study cohort	Age at baseline and sex	Stress task	Length of follow-up	Negative health outcomes assessed	Blunted Cardiovascular Parameter	Significant findings
<i>Adverse cardiovascular health (Healthy samples)</i>								
Brody and Rau (1994)	80	Healthy normotensives adult volunteers recruited from the local working population	Mean age: 31.4 34 female 46 male	Mental arithmetic task	19 months	1. Changes in resting SBP and DBP from baseline to follow-up	HR	1. Blunted HR reactivity predicted greater increases in resting DBP in adjusted analyses.
Heponiemi et al. (2007)	66	A sample of healthy adults who participated in the 1999 (Psychophysiology experiment) and the 2001 (intima-media thickness measure) follow-ups of the Cardiovascular Risk in Young Finns study (Cardiovascular Risk in Young Finns study)	Age: 30.73 (age at follow-up) 33 Female 33 Male	Mental arithmetic and speech task (Reactivity was averaged across tasks)	2–2.5 years	1. Carotid atherosclerosis assessed by intima-media thickness at a 2-year follow-up	HR	1. Blunted HR reactivity predicted greater intima-media thickness at a 2-year follow-up in unadjusted and adjusted analyses.
Matthews et al. (2006)	2816	Participants who competed year 2 and year 15 follow-ups of the Coronary Artery Risk Development in Young Adults Study Coronary Artery Risk Development in Young Adults Study	1527 female 1289 male Age: 20–35 years	Video game and star tracing mirror tracing task	13 years	1. Coronary calcification	HR	1. Participants with evidence of coronary calcification at the 13-year follow-up displayed blunted HR reactivity to the video game in unadjusted analyses. 2. Blunted HR reactivity predicted an increased risk of coronary calcification at the 13-year follow-up amongst black participants in adjusted analyses.
Brindle et al. (2016)	438	Participants who completed both 2002–2004 (stress testing) and the 2008–2009 sessions of the Dutch famine birth cohort study (Dutch famine birth cohort study)	Mean age: 58.4 230 female 208 male	Stroop, mirror tracing and speech tasks (Reactivity was averaged across tasks for main analyses)	5.5 years	1. Diagnosis of hypertension	HR (within cluster analysis)	1. In comparison to a cluster of exaggerated reactors (exaggerated SBP, DBP and HR reactivity), a cluster characterised by lower HR and equally exaggerated SBP and DBP were at increased risk of hypertension diagnosis in adjusted and unadjusted analyses. 2. Adjusted and unadjusted analyses for each task confirmed that the cluster characterised by lower HR and exaggerated SBP and DBP were at increased risk of hypertensive diagnosis in comparison to the cluster of exaggerated reactors (exaggerated SBP, DBP and HR reactivity) for both the speech and stroop tasks.
<i>Adverse cardiovascular health (Cardiac samples)</i>								

(Continued)

Table 2. Continued.

Authors/Year	Sample size for prospective analyses	Study population or name of study cohort	Age at baseline and sex	Stress task	Length of follow-up	Negative health outcomes assessed	Blunted Cardiovascular Parameter	Significant findings
Ahern et al. (1990)	341	Myocardial infarction patients with $\geq 10$ ventricular premature complexes/hour or $\geq 5$ episodes of nonsustained ventricular tachycardia. (The Cardiac Arrhythmia Pilot Study)	Not reported	Portable video game	1 year	1. Death or cardiac arrest	HR	1. Blunted HR reactivity predict death or cardiac arrest in adjusted analysis
Herd et al. (2003)	521	A sample of participants who underwent coronary artery bypass surgery 6 months prior to participant in the cardiovascular stress reactivity study. (Post coronary artery bypass graft biobehavioral study)	Mean age: 62 170 Female 351 Male	Mirror tracing task and speech task (The maximum change in response to the stress was used as reactivity)	2.5 years	1. Clinical events including death, acute myocardial infarction, cerebrovascular accident, new onset of angina pectoris.	HR, DBP	1. The quartile of participants with the lowest HR reactivity (4 beats/min or lower) had twice the rate of clinical events as patients in the quartile with the highest HR reactivity in adjusted analyses. 2. The quartile of participants with the lowest DBP reactivity (9 mm Hg or lower) had twice the rate of clinical events as patients in the quartile with the highest DBP reactivity in adjusted analyses.
Kupper et al. (2015)	100	A sample of patients with systolic heart failure and reduced left ventricular ejection fraction ( $<40\%$ as measured by echo or nuclear imaging study)	Mean age 66.6 26 Female 74 Male	Speech task	48.5 months	1. Mortality	DBP	1. Mortality rates were significantly greater amongst participants who exhibited blunted (1st quartile) DBP reactivity in comparison to participants who exhibited intermediate DBP responses (2nd and 3rd quartile) in partially and fully adjusted analyses
Sherwood et al. (2017)	199	Outpatients diagnosed with heart failure, with left ventricular ejection fraction $\leq 40\%$	Mean age 57.0 64 female 135 male	Speech task	5 years	1. Cardiovascular hospitalisation or death	SBP, DBP	1. Blunted SBP reactivity predicted an incidence risk of cardiovascular hospitalisation or death in partially and fully adjusted analyses. 2. The intermediate tertile of SBP reactivity was associated with an increased risk of cardiovascular hospitalisation or death in comparison to the higher tertile of SBP reactivity in adjusted analyses.** 3. Blunted DBP reactivity predicted an incidence risk of cardiovascular hospitalisation or death in partially and fully adjusted analyses. 4. The lower tertile of DBP reactivity was associated with an increased risk of cardiovascular hospitalisation or death in comparison to the intermediate tertile of DBP reactivity in adjusted analyses.

Motivational and behavioural dysregulation (all healthy samples)

Carroll et al. (2008)	1276	A large community sample who completed the third and fourth follow-ups of the West of Scotland twenty-07 study West of Scotland twenty-07 study- WOST07	Mean age: 41.8 700 female 576 male	PASAT	5.5 years	1. Becoming obese over the 5-year follow-up	HR	1. Blunted HR reactivity predicted an increased likelihood of becoming obese in unadjusted and adjusted analyses.
Phillips et al. (2012)	460	Participants who completed both 2002–2004 (stress testing) and the 2008–2009 sessions of the Dutch famine birth cohort study (Dutch famine birth cohort study)	Mean age: 58.3 240 female 220 male	Stroop, mirror tracing and speech tasks. Highest average task value was used for calculation of reactivity analyses.	4–7 years	1. Becoming or staying obese (BMI > 30 kg/m <sup>2</sup> ) vs. becoming or remaining non-obese at a 4–7-year follow-up	HR	1. Blunted HR reactivity predicted increased likelihood of becoming or staying obese at the follow-up in unadjusted and adjusted analyses.
Ginty et al. (2015)	176	Final year high school students in close proximity to the University of Birmingham	Mean age: 18.02 145 female 31 Male	PASAT	1.08years	1. Perseverance, operationalised as the failure to complete a subsequent 1-year follow-up assessment	HR	1. Non-completers of the study follow-up showed significantly lower HR reactivity than completers 2. Blunted HR reactivity predicted an increased odds of study non-completion in unadjusted and adjusted analyses
De Vries-Bouw et al. (2011)	68	Male adolescents attending a delinquency diversion programme after having committed a minor offense	Mean age: 13.9 All male	Public speaking task	5.5 Years	1. Reoffending rates at the 5-year follow up	HR	1. Blunted HR reactivity predicted a higher reoffending rate at the follow-up
Ginty et al. (2021)	120	A student sample	Mean age:19.39 87 female 33 Male	PASAT	1–15 months	1. PTSD symptoms in relation to the COVID-19 pandemic	HR	1. Blunted HR reactivity predicted greater levels of intrusion (e.g., intrusive cognitions and nightmares) in adjusted analyses. 2. Blunted HR reactivity predicted greater hyperarousal (e.g., anger and trouble concentrating) in adjusted analyses.
Halligan et al. (2006)	58	A sample of assault victims (assaulted within the last 3 months)	Mean age: 39.0 28 Female 33 male (Sex at baseline of 61 participants tested)	Assault recall task	6 months	1. Change in posttraumatic stress disorder (PTSD) symptoms over a 6-month follow-up	HR	1. Blunted HR reactivity predicted a lower reduction in PTSD symptoms a 6-month follow-up amongst participants with PTSD.

(Continued)

Table 2. Continued.

Authors/Year	Sample size for prospective analyses	Study population or name of study cohort	Age at baseline and sex	Stress task	Length of follow-up	Negative health outcomes assessed	Blunted Cardiovascular Parameter	Significant findings
Wangelin and Tuerk (2015)	18	Male combat PTSD veterans receiving prolonged exposure therapy in a Veterans affairs clinic	Mean age 32 All male	Script –driven imagery task	Session 2 to end of treatment (5-11 sessions) of prolonged exposure therapy. 7.6 session on average (Specific time not specified)	1. PTSD symptoms	HR	1. Blunted HR reactivity predicted less of a decrease in PTSD symptoms at post treatment.
Phillips, Hunt, et al. (2011)	1245	A large community sample who completed 3rd and 4 <sup>th</sup> follow-up of the West of Scotland twenty-07 study (West of Scotland twenty-07 study)	Mean age a: 42.3 686 female 559 male	PASAT	5.5 years	1. Anxiety and depressive symptoms at a 5-year follow-up	HR	1. Blunted HR reactivity predicted increased depression scores at the 5-year follow-up in unadjusted and adjusted analyses. 2. Blunted HR reactivity predicted increased anxiety scores at the 5-year follow-up in unadjusted analyses. 3. Blunted HR reactivity predicted increased likelihood of depression caseness (HADS $\geq$ 8) at the 5-year follow-up in unadjusted analyses. 4. Blunted HR reactivity predicted increased likelihood of anxiety caseness (HADS $\geq$ 8) at the 5-year follow-up in unadjusted analyses.
Phillips, Der, et al. (2011)	852	A large community sample who completed 3rd and 4th follow-up of the West of Scotland twenty-07 study (West of Scotland twenty-07 study)	Mean age: 51.9 459 female 393 male	PASAT	5.4 years	1. Change in disability scores over a 5-year follow-up	HR	1. Blunted HR reactivity predicted a greater deterioration (increase in disability score) over the 5-year follow-up in partially and fully adjusted analyses.
Lawler and Schmieid (1992)	32	A sample of female clerical workers	Mean age: 43.8 (age at follow-up) All female	Structured interview task	5 years	1. Illness frequency over the past 12 months	SBP	1. Blunted SBP reactivity predicted greater illness frequency over the past 12-months reported at the 5-year follow-up
al'Absi et al. (2005)	72	Healthy Smokers from the local community abstaining from smoking for 24 h before completing the laboratory session	Mean age: 36 33 female 39 Male	Speech task and mental arithmetic/ PASAT (Reactivity was averaged across tasks)	4 weeks	1. Relapse (relapse vs. successful quitters) 2. Time to relapse	DBP	1. Relapsers exhibited blunted DBP responses in comparison to successful quitters in unadjusted analyses. 2. Blunted DBP reactivity predicted faster time to relapse in adjusted and unadjusted multivariate regression analyses.

Ginty et al. (2011)	1170–1251 (5.5 year) 1148–1189 (12.4 year)	A large community sample who completed the third, fourth and fifth follow-ups of the West of Scotland twenty-07 study (West of Scotland twenty-07 study-WOST07)	Mean age: 42.2 5 year Female:641-677 Male: 529–574 10 year Female: 618–648 Male:530-541	PASAT	5.5 years and 12.4 years	1. General mental ability (Alice Heim -4) 2. Choice reaction time	HR,SBP	<ol style="list-style-type: none"> <li>1. Blunted HR reactivity predicted lower general mental ability at both a 5-year and 12-year follow-up in unadjusted and adjusted analyses</li> <li>2. General mental ability at both the 5-year and 12-year follow-up also significant varied across a HR reactivity tertile split. Those in the lowest tertile of HR reactivity had the lowest general mental ability scores.</li> <li>3. Blunted HR reactivity predicted slower choice reaction time at both a 5-year and 12-year follow-up in unadjusted and adjusted analyses.</li> <li>4. Choice reaction time at both the 5-year and 12-year follow-up also significant varied across a HR reactivity tertile. Those in the lowest tertile of HR reactivity had the slowest reaction time.</li> <li>5. Blunted SBP reactivity predicted slower choice reaction time at a 5-year follow-up in adjusted analyses.</li> <li>6. Blunted HR reactivity predicted lower numerical and verbal reasoning scores at a 5-year and 12-year follow-up in adjusted analyses.</li> <li>7. Blunted HR reactivity predicted a greater decline in general mental ability, and a greater increase (slower) in choice reaction time from the 5-year to the 12-year follow-up in adjusted and unadjusted models.</li> <li>8. Change in choice reaction time between the 5-year and 12-year follow-up also significantly varied across a HR reactivity tertile split. Those in the lowest tertile of HR reactivity showed the greatest increase (slower) in choice reaction time.</li> <li>8. The effect of blunted reactivity on change in choice reaction time was most pronounced amongst the oldest age cohort of participants</li> </ol>
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(Continued)

Table 2. Continued.

Authors/Year	Sample size for prospective analyses	Study population or name of study cohort	Age at baseline and sex	Stress task	Length of follow-up	Negative health outcomes assessed	Blunted Cardiovascular Parameter	Significant findings
Yano et al. (2016)	3021	Participants who competed year 2 and year 25 follow-ups of the Coronary Artery Risk Development in Young Adults Study CARDIA study	Mean age: 27.1 1698 female 1323 male	Video game and a start tracing mirror image task	23 years	1. Cognitive function including psychomotor speed, verbal memory and executive skills	SBP, DBP	<ol style="list-style-type: none"> <li>1. The lower deciles of SBP reactivity to the both the star tracing and video game tasks was associated with poorer psychomotor speed and executive skills at the 23-year follow-up in partially adjusted analyses.</li> <li>1. The lower deciles of DBP reactivity to the star tracing task was associated with poorer psychomotor speed at the 23-year follow-up in partially adjusted analyses.</li> <li>2. Blunted SBP reactivity to the star tracing task and the video game tasks predicted poorer psychomotor speed at the 23-year follow-up in unadjusted, partially adjusted and fully adjusted analyses.</li> <li>4. Blunted DBP reactivity to the star tracing task predicted poorer psychomotor speed at the 23-year follow-up in unadjusted, partially adjusted and fully adjusted analyses.</li> <li>5. Blunted SBP reactivity to the star tracing task predicted poorer verbal memory at the 23-year follow-up in unadjusted analyses.</li> <li>6. Blunted SBP reactivity to the video game task predicted poorer verbal memory at the 23-year follow-up in partially adjusted analyses.</li> <li>7. Blunted DBP reactivity to the video game task predicted poorer verbal memory at the 23-year follow-up in partially adjusted and fully adjusted analyses.</li> <li>8. Blunted SBP reactivity to the star tracing task and video game tasks predicted poorer executive skills at the 23-year follow-up in unadjusted, partially adjusted and fully adjusted analyses.</li> </ol>
Yuenyongchaiwat and Sheffield (2017)	102	Healthy adult (student and staff) participants from the local University	Mean age: 31.43 75 female 27 male	Mental arithmetic and Speech task	40.98 months	1. Anxiety	HR, SBP	<ol style="list-style-type: none"> <li>1. Blunted SBP reactivity to the mental arithmetic stress task predicted increased anxiety scores at the 40-month follow-up in unadjusted and adjusted analyses.</li> <li>2. Blunted HR reactivity to the mental arithmetic stress task predicted increased anxiety scores at the 40-month follow-up in unadjusted analyses.</li> </ol>

Phillips et al. (2009)	1318	A large community sample who completed the 3rd and 4th follow-up of the West of Scotland twenty-07 study (West of Scotland twenty-07 study)	Mean: 41.8 890 Female 757 Male (Sex at baseline of 1647 participants tested)	PASAT	5.5 years	1. Self-reported health at a 5-year follow up	HR,SBP,DBP	<ol style="list-style-type: none"> <li>1. Blunted HR reactivity predicted poorer self – reported health (excellent/good vs. fair/poor) at the 5-year follow-up (deterioration in health) in partially and fully adjusted analyses.</li> <li>2. Blunted SBP reactivity predicted poorer self – reported health (excellent/good vs. fair/poor) at the 5-year follow-up (deterioration in health) in partially adjusted analyses.</li> <li>3. Blunted DBP reactivity predicted poorer self –reported health (excellent/good vs. fair/poor) at the 5-year follow-up (deterioration in health) in partially and fully adjusted analyses.</li> <li>4. The bottom quartile of HR reactivity reported poorer health (excellent/good vs. fair/poor) at the 5 year follow- in comparison to the top quartile of HR reactivity in unadjusted analyses.</li> <li>5. The bottom quartile of SBP reactivity reported poorer health (excellent/good vs. fair/poor) at the 5 year follow- in comparison to the top quartile of SBP reactivity in unadjusted analyses.</li> <li>6. The bottom quartile of DBP reactivity reported poorer health (excellent/good vs. fair/poor) at the 5 year follow- in comparison to the top quartile of DBP reactivity in unadjusted analyses.</li> <li>7. Blunted HR reactivity predicted poorer self – reported health (excellent vs. good vs. fair vs. poor) at the 5-year follow-up (deterioration in health) in partially adjusted analyses.</li> <li>8. Blunted SBP reactivity predicted poorer self – reported health (excellent vs. good vs. fair vs. poor) at the 5-year follow-up (deterioration in health) in partially adjusted analyses.</li> <li>9. Blunted DBP reactivity predicted poorer self –reported health (excellent vs. good vs. fair vs. poor) at the 5-year follow-up (deterioration in health) in partially adjusted analyses.</li> </ol>
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\*\*The intermediate SBP response of 19.00 mmHg was not included in the computation of cardiovascular reactivity ranges. This value represents the intermediate tertile of reactivity, which predicted a greater risk of cardiovascular hospitalisation or death in comparison to the high tertile of reactivity. There was no difference in cardiovascular hospitalisation or death between the intermediate and low tertile of SBP reactivity, indicating that the low and intermediate groups had a similar risk of adverse cardiovascular outcomes. However, the authors did not report the mean response of these groups together. Therefore, this response is unlikely to represent the overall lower or blunted response that predicted adverse cardiovascular outcomes.

**Table 3.** Thresholds of blunted cardiovascular reactivity that predicted adverse cardiovascular health.

Authors	Sample size for prospective analyses	Sample	Stress task	Length of follow-up	Negative health outcomes assessed	Threshold of Blunted Reactivity	Note on mean blunted response	Sample response	Percent change of blunted compared to sample
Ahern et al. (1990)	341	Cardiac sample	Portable video game	1 year	Death or cardiac arrest	HR: 4.00 BPM	The mean HR reactivity (at baseline) of participants who died or experienced cardiac arrest at the follow-up was considered blunted	HR: 7.31 BPM Calculated as the combined sample weighted mean of the two groups (death or cardiac arrest versus no death or cardiac arrest)	45.28% <i>less</i> than the sample mean
Kupper et al. (2015)	100	Cardiac sample	Speech task	48.5 months	Mortality	DBP: -2.4 mmHg	The mean DBP response of the lower quartile of DBP reactivity, which was found to predict mortality in heart failure patients was considered blunted.	DBP: 7.1 mmHg Mean sample reactivity reported in article	133.80% <i>less</i> than the sample mean
Matthews et al. (2006)	2816	Healthy sample	Video game and star tracing mirror tracing task	13 years	Coronary calcification	HR: 4.4 bpm	The mean HR reactivity of participants who had coronary calcification at the follow-up was considered blunted.	HR: 5.40BPM Calculated as the combined sample weighted mean of the two groups (any calcification versus no evidence of calcification)	18.52% <i>less</i> than the sample mean
Sherwood et al. (2017)	199	Cardiac sample	Speech task	5 years	Cardiovascular hospitalisation or death	**SBP: 19.00 mmHg DBP: 5.00 mmHg	The mean SBP reactivity for the intermediate tertile and the mean DBP reactivity for the low tertile, which were found to predict cardiovascular hospitalisation or death was considered blunted.	**SBP: 19.40mmHg DBP: 14.7 mmHg Mean sample reactivity reported in article	DBP reactivity only: 65.99% <i>less</i> than the sample mean

\*\*The intermediate SBP response of 19.00 mmHg was not included in the computation of cardiovascular reactivity ranges. This value represents the intermediate tertile of reactivity, which predicted a greater risk of cardiovascular hospitalisation or death in comparison to the high tertile of reactivity. There was no difference in cardiovascular hospitalisation or death between the intermediate and low tertile of SBP reactivity, indicating that the low and intermediate groups had a similar risk of adverse cardiovascular outcomes. However, the authors did not report the mean response of these groups together. Therefore, this response is unlikely to represent the overall lower or blunted response that predicted adverse cardiovascular outcome

**Table 4.** Thresholds of blunted cardiovascular reactivity that predicted non-cardiovascular outcomes (Motivational/Behavioural dysregulation).

Authors/	Sample size for prospective analyses	Sample	Stress task	Length of follow-up	Negative health outcomes assessed	Threshold of Blunted Reactivity	Note	Sample response	Percent change of blunted compared to sample
Carroll et al. (2008)	1276	Healthy sample	PASAT	5.5 years	Becoming obese	HR: 6.8bpm	The mean HR reactivity for participants who became obese was considered blunted.	HR: 8.2bpm Mean reactivity for this sample was reported in a separate paper	17.07% less than the sample mean
Ginty et al. (2015)	176	Healthy sample	PASAT	1.08 years	Perseverance, operationalised as the failure to complete a subsequent 1-year follow-up assessment	HR: 12.59 bpm	The mean HR reactivity of participants who did not complete the study was considered blunted	HR: 16.19 Calculated as the combined sample weighted mean of the two groups (completers versus non-completers). Difference between mean baseline and mean stress tasks values reported also yield identical reactivity estimations.	22.24% less than the sample mean
Phillips et al. (2009)	1318	Healthy sample	PASAT	5.5 years	Self-reported health	HR: -3.0 Bpm SBP: -2.7 mmHg DBP: -2.2 mmHg	The mean response of the bottom quartile of HR, SBP and DBP reactors, which was found to predict poorer self-reported health was considered blunted.	HR: 8.2 SBP: 11.6 DBP: 7.0 Mean reactivity for this sample was reported in a separate paper	HR: 136.59% less than the sample mean SBP: 123.28% less than the sample mean DBP: 131.43% less than the sample mean
Phillips et al. (2012)	460	Healthy sample	Stroop, mirror tracing and speech tasks.	4-7 years	1. Becoming or staying obese (BMI > 30 kg/m <sup>2</sup> ) vs. becoming or remaining non-obese	HR: 10.1 bpm	The mean HR reactivity for participants who became or remained obese at the follow-up was considered blunted.	HR: 11.8 Mean sample reactivity reported in article	14.41% less than the sample mean

2015), increased delinquent reoffending rates (De Vries-Bouw et al., 2011), increased post-traumatic stress disorder symptoms as well as a smaller reduction in symptoms (Ginty et al., 2021; Halligan et al., 2006; Wangelin & Tuerk, 2015), anxiety (Phillips, Hunt, et al., 2011; Yuenyongchaiwat & Sheffield, 2017), depression (Phillips, Hunt, et al., 2011), and self-reported physical disability (Phillips, Der, et al., 2011).

Blunted SBP reactivity predicted increased self-reported illness frequency over the past 12 months (Lawler & Schmied, 1992). Blunted DBP reactivity predicted an increased likelihood of smoking relapse and faster time to relapse (al'Absi et al., 2005). Both blunted SBP and HR reactivity predicted cognitive decline/poor cognitive functioning (Ginty et al., 2011; Yano et al., 2016), and elevated anxiety (Yuenyongchaiwat & Sheffield, 2017). Finally, blunted SBP, DBP, and HR reactivity predicted poorer self-reported general health (Phillips et al., 2009).

### **Threshold of blunted cardiovascular reactivity for non-cardiovascular outcomes**

Blunted HR reactivity was found to be the most predictive cardiovascular parameter of non-cardiovascular health outcomes. A total of 12 (80.00%) studies found an effect of blunted HR reactivity on prospective outcomes. In comparison, five (33.33%) studies found an effect of SBP reactivity, and three (20.0%) studies found an effect of DBP reactivity.

Of these 15 studies, the value of a mean blunted response could be extracted for four studies (See Table 4). A cardiovascular response equal to or lower than values on HR reactivity between  $-3.00$  bpm and  $12.59$  bpm appears to predict adverse non-cardiovascular related outcomes. A lack of mean blunted responses reported for SBP and DBP across studies precluded the computation of ranges for these cardiovascular parameters.

The mean blunted cardiovascular response that predicted adverse cardiovascular health outcomes ranged between  $14.41\%$  and  $136.59\%$  lower than the sample mean for HR reactivity.

## **Discussion**

This systematic review confirms that blunted cardiovascular reactivity to psychological stress predicts a broad range of outcomes, including health, behavioural, and cognitive indicators of well-being. Thus, lower or blunted cardiovascular responses to psychological stress are not benign, but instead, predict adverse cardiovascular outcomes, as well as outcomes proposed to be associated with motivational and behavioural dysregulation. Importantly, however, blunted reactivity appears to have different consequences depending on the sample examined. In individuals with an existing cardiovascular condition, blunted cardiovascular reactivity is, perhaps unsurprisingly, predictive of adverse cardiovascular health, including death. In healthy samples, blunted reactivity is more consistently associated with non-cardiovascular related outcomes. Importantly, our review identifies sensitive threshold levels for both HR and DBP reactivity that confer increased risk of adverse health outcomes, as well as outcomes associated with motivational and behavioural dysregulation.

Twelve studies identified in the current review were also included in the systematic review conducted by Turner et al. (2020). Of the 47 studies included by Turner et al. (2020), 17 reported an effect of blunted reactivity on prospective health outcomes. The additional 5 studies pertaining to blunted reactivity included in their review examined parameters other than SBP, DBP or HR reactivity (e.g., plasma cortisol, salivary cortisol, adrenaline) (Flaa et al., 2008; Paananen et al., 2015; Ronaldson et al., 2016; Steudte-Schmiedgen et al., 2015; Zhu et al., 2016). We identified an additional 11 studies that were not included in the synthesis of blunted reactivity in this previous review. The inclusion of these additional studies was primarily due to differences pertaining to inclusionary criteria, and indicated that blunted reactivity has predictive utility for health outcomes in cardiac populations (Ahern et al., 1990; Herd et al., 2003; Kupper et al., 2015; Sherwood et al., 2017) and outcomes at a follow-up  $\leq 1$  year (al'Absi et al., 2005; Halligan et al., 2006; Wangelin & Tuerk, 2015). Remaining articles we identified found blunted reactivity to predict lower perseverance (Ginty et al., 2015),

delinquent reoffending (De Vries-Bouw et al., 2011), and PTSD symptoms (Ginty et al., 2021). Finally, while Turner et al. (2020) included the study findings reported by Brindle et al. (2016), they did not include these results in the synthesis of findings pertaining to blunted stress reactivity.

Of the 23 studies reporting an effect of blunted cardiovascular reactivity on health outcomes, 10 mean blunted responses could be extracted from eight studies. Statistical design (correlational) was the primary reason for not reporting a blunted response. While a continuous association between cardiovascular reactivity and health outcomes allows lower/blunted responding to be associated with prospective health, it does not lend itself to this establishment of a 'point' of blunted reactivity. These threshold levels will have utility to guide future research and will enable researchers to determine if reduced cardiovascular responses exhibited in cross-sectional studies are indicative of adverse health outcomes. Moreover, these thresholds are particularly relevant for clinicians, to be used as an early diagnostic screening tool of blunted reactors, who are vulnerable to poorer prognosis and increased risk of negative cardiac events. Further, while our review found that several studies reported blunted SBP reactivity to predict adverse health outcomes, a lack of mean blunted responses reported for SBP in these studies precluded the computation of ranges for this cardiovascular parameter.

In healthy samples, blunted HR reactivity was the only parameter associated with adverse cardiovascular outcomes, indicating that HR reactivity may be an important parameter in the prediction of cardiovascular disease development. However, methodological issues limited many of these studies. While Matthews et al. (2006) reported blunted HR reactivity to predict coronary calcification, these results became non-significant in adjusted analyses, with results remaining significant in adjusted analyses only amongst Black participants. Additionally, HR was measured only once during exposure to the stress task, and therefore it is not possible to assess the reliability of the measure, nor be sure that it adequately encapsulates the entirety of the stress response. Similarly, Brindle et al. (2016) found that in comparison to a cluster of exaggerated reactors (exaggerated SBP, DBP and HR reactivity), a cluster characterised by lower HR but *equally* exaggerated SBP and DBP were at increased risk of hypertension diagnosis in adjusted and unadjusted analyses. While difference in hypertension diagnosis appeared to be due to differences in reactivity between groups on HR, this cannot be definitively concluded from a cluster analysis. The increased risk of hypertension may have been due to the combination (interaction effect) of lower HR reactivity with higher SBP and DBP reactivity, not due to lower HR reactivity alone. In fact, this would appear to be the case given that the cluster characterised by the lowest response on blood pressure and HR were not at increased risk of hypertension diagnosis. Finally, Heponiemi et al. (2007) found blunted HR reactivity to predict greater intima-media thickness at a 2-year follow-up. However, this study failed to examine change scores nor did it adjust for intima-media thickness at baseline. Thus, conclusions pertaining to cause and effect cannot be deduced as the association between lower reactivity and intima-media thickness may have been present at baseline. Therefore, evidence linking blunted cardiovascular reactivity to adverse cardiovascular health in *healthy populations* is limited by methodological issues and findings should be taken tentatively.

However, in cardiac samples, blunted HR, SBP and DBP reactivity predicted a range of adverse cardiovascular outcomes including cardiac arrest, myocardial infarction, angina, cerebrovascular events, cardiovascular hospitalisation and death in methodologically sound studies (Ahern et al., 1990; Herd et al., 2003; Kupper et al., 2015; Sherwood et al., 2017). Thus, blunted cardiovascular reactivity appears to be an important predictor of poor prognosis in cardiac samples. One likely explanation for these findings is that blunted cardiovascular reactivity signifies an inadequacy of the cardiovascular system to produce a sufficient cardiovascular response (i.e., chronotropic incompetence) due to existing cardiovascular conditions. Therefore, blunted cardiovascular reactivity to psychological stress likely serves as a marker of disease severity amongst cardiac patients.

Many cardiovascular diseases (predominately heart failure) are characterised by chronotropic and inotropic incompetence, resulting in a reduced ability of the heart to produce cardiovascular responses to meet metabolic demands during various exertion (reduced ability to facilitate

oxygen uptake ( $VO_2$  consumption) (Brubaker & Kitzman, 2011; Zweerink et al., 2018). Moreover, chronotropic incompetence in cardiac populations is a fundamental predictor of reduced functional capacity, disease severity and mortality (Dobre et al., 2013; Magri et al., 2014). Thus, blunted cardiovascular reactivity to stress may be indicative of augmented chronotropic incompetence, whereby the heart fails to meet metabolic demands during mental exertions. In fact, others have posited that this type of below-normal chronotropic stress response in cardiac populations are engendered by inadequate functioning of the left ventricle (Herd et al., 2003; Kupper et al., 2015), which is solely responsible for pumping oxygen-rich blood to tissues of the body via the aorta, to meet bodily needs. Therefore, chronotropic incompetence is a likely direct pathophysiological mechanism linking blunted cardiovascular reactivity to inauspicious cardiovascular outcome, particularly in cardiac populations.

Furthermore, unlike the exaggerated cardiovascular reactivity literature, whereby exaggerated SBP reactivity has been noted as particularly toxic and a predictive marker of poor cardiovascular health (Barnett et al., 1997; Carroll et al., 2003), as well as mortality (Carroll, Ginty, Der, et al., 2012), blunted HR reactivity was the most common reactivity predictor of negative cardiovascular outcomes. Chronotropic incompetence is propounded to result from chronic sympathetic over-activation, which leads to downregulation and desensitisation of cardiac beta-adrenergic receptors of the sinoatrial node, resulting in a diminished ability of the myocardium to increase HR to meet metabolic demands (Brubaker & Kitzman, 2011; Zweerink et al., 2018). Therefore, it is likely that blunted HR reactivity is the most reliable cardiovascular parameter that reflects augmented desensitisation/downregulation of cardiac beta-adrenergic receptors and a reduced ability to meet metabolic demands, and therefore, poorer cardiovascular health outcomes.

A second cluster of outcomes predicted by blunted reactivity pertained non-cardiovascular outcomes, which were all proposed markers of deficits in motivation and behavioural regulation. Interestingly, many of these cognitive and behavioural factors predicted by blunted reactivity including depression, anxiety, post-traumatic stress disorder, obesity, poorer perseverance and addiction (e.g., smoking), criminal offending (e.g., delinquent reoffending), and reduced cognitive ability are all linked to poorer cardiovascular health (Cohen et al., 2015; Donahue, 2014; Ezzati et al., 2005; Shipley et al., 2008; Wilson et al., 2002). Thus, in addition to a direct effect on cardiovascular health, blunted cardiovascular reactivity may also signal an increased risk of adverse cardiovascular outcomes via several cardiovascular risk factors associated with deficits in motivational and behavioural regulation.

The association between blunted reactivity and these markers of motivational and behavioural dysregulation is premised on sub-optimal functioning of the fronto-limbic system (Carroll et al., 2017; Lovallo, 2011; Phillips et al., 2009; Phillips et al., 2013). Neuroimaging studies have implicated reduced activation or greater deactivation in several areas of the fronto-limbic system as fundamental determinants of blunted cardiovascular reactivity, including the amygdala, insular cortex, anterior cingulate cortex (anterior mid-cingulate and the perigenual/pregenual anterior cingulate regions), posterior cingulate cortex, and the pre-frontal cortex (dorsolateral, medial pre-frontal regions) (Gianaros et al., 2005; Gianaros et al., 2008; Ginty et al., 2013; Wager et al., 2009). Furthermore, research suggests that it is poorer functional connectivity between several of these areas that engender the blunted cardiovascular stress responses (Gianaros et al., 2008; Ginty et al., 2019).

These neuroanatomical areas are responsible for motivational processing, regulating goal-driven behaviours and reward-based decision-making (Devinsky et al., 1995; Holroyd & Yeung, 2012; Jumah & Dossani, 2020; Kim, 2013). Thus, inadequate functioning of these areas may result in withdrawal and disengagement with the psychological stress task due to diminished motivation, resulting in blunted cardiovascular reactivity. In fact, others have suggested that blunted cardiovascular reactivity may be due to a motivational disengagement during performance situations (i.e., absence of task engagement) (Hase et al., 2020). Reduced activation in these aforementioned neuroanatomical areas have also been linked to a myriad of adverse psychological states, as well as addiction and obesity (Brooks et al., 2013; Etkin & Wager, 2007; Fitzgerald et al., 2008; Kaufman et al., 2003;

Nestor et al., 2011; Stevens et al., 2011). Thus, blunted cardiovascular reactivity to stress is likely a marker of central motivational and behavioural dysregulation caused by suboptimal functioning of neuroanatomical regions localising in the fronto-limbic system, which may engender vulnerability to adverse behavioural, motivational and psychological states which rely on adequate functioning of these areas (Carroll et al., 2017). In turn, these behavioural, motivation and psychological states infer increased risk of cardiovascular disease outcomes.

Blunted cardiovascular reactivity is likely dependant on differential processes in cardiac and health samples. In cardiac samples, blunted cardiovascular reactivity was solely found to predict adverse cardiovascular outcomes. However, in healthy samples blunted cardiovascular reactivity was primarily found to predict outcomes associated with deficits in motivational and behavioural regulation; the association between blunted cardiovascular reactivity and prospective cardiovascular outcomes in healthy samples was weak. Thus, in cardiac samples blunted cardiovascular reactivity is likely due to an inability of the heart to produce adequate cardiovascular responses to meet the metabolic demands of the stress task (i.e., chronotropic incompetence). Whereas, in healthy samples, blunted cardiovascular reactivity is likely engendered by suboptimal functioning of neuroanatomical regions localising in the fronto-limbic system, responsible for motivational and behavioural regulation.

One major strength of the current review pertains to the systematic process. Prior summaries of the blunted cardiovascular reactivity literature have primarily employed narrative reviews or article overviews (Carroll et al., 2009; Carroll et al., 2017; Phillips et al., 2013), whereby the main corollaries of blunted reactivity are discussed. The systematic process employed in the current review has allowed us to encapsulate a broader scope of health and other outcomes associated with blunted reactivity. This has also allowed the identification of important differences in the associations of blunted reactivity in clinical and healthy samples, as well as extending the theoretical predictive utility of blunted cardiovascular reactivity to cardiovascular outcomes. Secondly, we synthesised prospective/longitudinal studies whereby cardiovascular reactivity was assessed at baseline, and the health/behavioural status at the follow-up period, providing strong evidence of the direction of the association between blunted reactivity and health. Thus, these findings indicate that blunted cardiovascular reactivity can promote poorer health, behavioural and psychological outcomes. More specifically, it is likely that the processes (neuroanatomical functioning and chronotropic incompetence) that blunted reactivity reflects cause these poorer outcomes, not the blunted response itself. We believe that blunted cardiovascular reactivity is a peripheral marker of (1) an inability of the heart to produce adequate responses to meet metabolic demands, and (2) sub-optimal functioning of neuroanatomical areas localising in the front limbic system responsible for motivation and behavioural regulation, which in turn promote poorer cardiovascular outcomes, as well as outcomes associated with deficits in motivational and behavioural regulation.

One limitation of the current review is that we did not examine the totality of evidence of the effect of blunted reactivity on each particular outcome. Prior cardiovascular reactivity reviews have included all studies examining the influence of reactivity on a particular outcome. The accumulation of positive, negative and null-findings are used to determine if a significant effect exists across studies, as well as the direction of this effect (Chida & Steptoe, 2010). Our a priori research question was to determine at what quantifiable point does a blunted response significantly predict adverse outcomes? This differs from a review conducted to establish if blunted reactivity predicted each outcome across studies. Thus, the inclusion of null-findings and positive findings (exaggerated reactivity on health), would bias the ranges of blunted responses provided via the inclusion of (1) mean responses that did not significantly predict outcomes and (2) increased mean responses that positively predicted health outcomes (exaggerated reactivity). While this was beyond the scope and research question of the current study, future reviews should employ meta-analytical procedures to determine if cardiovascular reactivity to stress significantly predicted each outcome across positive, negative and null study findings in the literature. While the majority of studies scored highly on the risk of bias and quality assessment, three studies received scores of 13/20 (Ahern et al., 1990;

**Table 5.** Recommended direction for future research.

Theme	Directions for future research
Predictive utility of cut-offs	Longitudinal studies should test the predictive utility of the blunted cut-offs for prospective health, behavioural and psychological outcomes. These studies should examine both raw and percentage change score cut-offs in a range of cohorts and in response to various stressors.
Corollaries of blunted reactivity	Cross-sectional studies examining the corollaries of blunted cardiovascular reactivity (e.g., neuroticism, Type D personality, disordered eating) should conduct follow-up analyses to identify if these corollaries predict classification of blunted cardiovascular reactivity using the cut-offs provided here (blunted versus non-blunted).
Thresholds of exaggerated reactivity	Future studies should aim to identify thresholds of exaggerated cardiovascular reactivity to stress. This would extend on the findings of the current study and would greatly enhance the field by enabling researchers to determine if responses to stress are exaggerated, blunted or normative.
Metabolic uncoupling of blunted reactivity	Future research should aim to identify if blunted cardiovascular reactivity is a metabolically uncoupled response, whereby the blunted response is lower than that predicted based on oxygen consumption. This may be particularly relevant for individuals with an existing cardiovascular condition, who may be unable to produce adequate cardiovascular responses to meet the metabolic demands of the stress task.

Wangelin & Tuerk, 2015; Yano et al., 2016) and two studies received scores of 12/20 (Heponiemi et al., 2007; Matthews et al., 2006). Thus, the findings from these studies should be taken tentatively. Finally, several papers in the literature utilised data from larger cohort studies, with two studies reporting results from the Dutch Famine Birth Cohort Study, five studies reporting results from the West of Scotland twenty-07 study and two studies reporting findings from the Coronary Artery Risk Development in Young Adults Study. This somewhat limits the generalisability of findings pertaining to blunted cardiovascular reactivity to other populations. Thus, future research should investigate if these findings can be replicated in other cohorts and populations.

Furthermore, the use of raw cardiovascular reactivity scores as a potential screening criteria for blunted cardiovascular reactivity may be somewhat confounded by the differential perturbations of cardiovascular activity across populations due to sample characteristic (e.g., age and sex) and varying stressors (e.g., speech versus mental arithmetic) (see Brindle et al., 2014). This is a standing limitation of the field, as what may be considered a blunted cardiovascular response (and a normative response) may vary depending on the cohort under investigation and the psychological stressor employed. However, we also provide a percentage change score of blunted cardiovascular reactivity in relation to the overall sample mean. This will enable researchers to identify if responses may be considered blunted relative to the sample from which they are drawn, and may be used as a confirmatory or alternative criteria to identify blunted cardiovascular reactivity.

While we have provided ranges of blunted reactivity that predict adverse outcomes, a healthy, or normative, response has yet to be determined. Future research should determine at what point increased cardiovascular reactivity (exaggerated reactivity) predicts negative health outcomes. This would enable researchers to identify a magnitude of reactivity which can be considered normative and benign. Additionally, with regard to cardiovascular disease, this would enable the distinction of metabolically uncoupled cardiovascular responses (exceeding [exaggerated] and not meeting [blunted] bodily demands), which promote adverse cardiovascular health, from responses that are metabolically justified. Furthermore, given the findings of the current review, we have provided recommendations for future directions and remaining questions in the field that researchers could address (see Table 5).

In sum, the current study suggests that blunted cardiovascular reactivity predicts poor cardiovascular health outcomes, particularly amongst individuals with a pre-existing cardiovascular condition, as well as outcomes associated with deficits in motivational and behavioural regulation in healthy populations. While the long-standing 'reactivity hypothesis' asserts that exaggerated cardiovascular reactivity to stress promotes poorer cardiovascular health, we confirm that blunted cardiovascular reactivity should not be considered benign. In the first paper to identify these

clinically relevant thresholds of blunted reactivity, we find that these thresholds are predictive of both poorer prospective cardiovascular health as well as outcomes associated with motivational and behavioural dysregulation, providing evidence for both direct and indirect effects on cardiovascular health. We posit that blunted reactions lower than, or equal to, the ranges reported here may be utilised by clinicians and researchers to identify individuals who are at increased risk of adverse cardiovascular health outcomes, as well as outcomes associated with motivational and behavioural dysregulation.

## Note

1. While it was the combination of high SBP and DBP reactivity, paired with lower HR reactivity, that predicted the development of hypertension, those who showed the lowest blood pressure and HR responses were not at increased risk of hypertension development.

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