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1 Cardiovascular Reactivity Patterns and Pathways to Hypertension: A Multivariate Cluster
2 Analysis

3 RUNNING HEAD: REACTIVITY PATTERNS AND HYPERTENSION

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Abstract

Substantial evidence links exaggerated mental stress induced blood pressure reactivity to future hypertension but the results for heart rate reactivity are less clear. For this reason multivariate cluster analysis was carried out to examine the relationship between heart rate and blood pressure reactivity *patterns* and hypertension in a large prospective cohort (age range 55-60 years). Four clusters emerged with statistically different systolic and diastolic blood pressure and heart rate reactivity patterns. Cluster 1 was characterised by a relatively exaggerated blood pressure and heart rate response while the blood pressure and heart rate responses of cluster 2 were relatively modest and in line with the sample mean. Cluster 3 was characterised by blunted cardiovascular stress reactivity across all variables and cluster 4, by an exaggerated blood pressure response equal to that of cluster 1 and a modest heart rate response equal to that of cluster 2. Membership to cluster 4 conferred an increased risk of hypertension at five year follow-up, HR = 2.98 (95%CI: 1.50-5.90), $p < .01$, that survived adjustment for a host of socio-demographic variables. These results further specify the established link between blood pressure reactivity and hypertension and support the use of multivariate approaches to stress psychophysiology.

Keywords: Psychological Stress, Multivariate Cluster Analysis, Hypertension, Blood Pressure, Heart Rate, Body Mass Index

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Introduction

96 The association between exaggerated blood pressure (BP) reactions to acute
97 psychological stress and hypertension is well established. Supporting evidence comes from
98 several independent epidemiological datasets that have shown exaggerated systolic (SBP)
99 and/or diastolic (DBP) BP reactivity to acute psychological stress to be linked with increased
100 resting BP at 6.5- and 12-year follow-up¹⁻² and to predict hypertension diagnosis at 13-year
101 follow-up³. In addition, being “high risk” for developing hypertension based on parental
102 history or having elevated resting BP are associated with exaggerated BP stress reactivity⁴.
103 Importantly, a large meta-analysis also has established a positive association between BP
104 stress reactivity and hypertension⁵.

105 In contrast, the relationship between stress-induced heart rate (HR) reactivity and
106 hypertension remains equivocal. Relatively increased HR reactivity has been observed
107 among individuals with parental history of hypertension⁶ and several small scale studies have
108 reported a positive association between HR stress reactivity and increased 1-year ambulatory
109 SBP⁷ and incident mild hypertension⁸. However, a relationship between HR reactivity and
110 elevated BP has failed to emerge from epidemiological studies³ or meta-analysis⁵. Further
111 complexity is added by findings of negative associations between HR stress reactivity and
112 hypertension risk factors such as obesity and the use of addicting substances such as alcohol
113 and tobacco. In each case, the obese⁹, smokers¹⁰, and those dependent on alcohol¹¹ all
114 exhibited blunted rather than exaggerated HR responses to acute psychological stress.
115 Accordingly, it may be timely to take a more nuanced look at the relationship between
116 cardiovascular stress reactivity and hypertension.

117 It has been suggested that focusing on a single cardiovascular reactivity variable may
118 be limiting in scope, as evidence has shown that different patterns of end-organ responses
119 have differential risk for disease¹² and that focusing on multivariate patterns of stress

120 reactivity may be more informative¹². With regard to BP and HR this makes sense given that
121 these variables are not independent but, in fact, profoundly influence each other; increases in
122 cardiac output increase BP and changes in BP influence HR via baroreceptor mechanisms¹³.
123 However, the wide interindividual variation in normal patterns of HR and BP stress responses
124 makes it challenging to define homogeneous groups of subjects. Cluster analysis offers a
125 solution to this problem by assigning subjects from a single large cohort into clusters based
126 on their statistical similarity on a set of variables defined *a priori*. This approach was
127 undertaken with two goals: 1) to identify clusters of individuals who exhibit significantly
128 different patterns of BP and HR stress reactivity, and 2) assess whether membership to a
129 particular cluster conferred increased/decreased risk of hypertension diagnosis at 5-year
130 follow-up.

131 **Methods**

132 **Participants**

133 Participants were from the Dutch Famine Birth Cohort, which comprised 2414 men
134 and women born in Amsterdam during 1943-1947. The study was designed to examine the
135 health consequences of prenatal famine exposure. Hence, it may be suggested that this
136 population characteristic may limit the generalizability of the present study results. However,
137 this is unlikely as, predominantly, famine exposure early in gestation, defined as a 13 week
138 period where daily caloric intake was below 1000 calories¹⁴ (Roseboom, van der Meulen,
139 Raveli, Osmond, Barker, & Bleker, 2001), was associated with poorer adult health¹⁵
140 (Roseboom, Painter, van Abeelen, Veenendaal, & de Rooij, 2011); only 58 (8.6%)
141 individuals in the present sample were exposed to famine during early gestation. **Reasons for**
142 **loss at follow-up include: 160 babies were not registered in Amsterdam, 328 individuals had**
143 **died at follow-up, 213 had emigrated, 157 refused to have their addresses collected, 125 were**
144 **untraceable at follow-up, and 8 requested to be removed from the study database^{16,17}. All**

145 1423 members of the cohort who lived in the Netherlands on September 1, 2002 were invited
146 to the clinic to undergo stress testing from 2002-2004; 740 attended. Follow-up analyses
147 comparing individuals who refused to participate in the stress testing wave (n = 683) with
148 those who participated in the follow-up showed that there were no differences in sex ($p = .49$)
149 or birth weight ($p = .42$). There was a significant difference in age (mean_{refused} = 58.3yrs,
150 mean_{attended} = 59.2yrs, $p < .01$).

151 In the 2008-2009 follow-up interviews were conducted. Participants self-reported
152 reported whether or not they had ever received a diagnosis of hypertension from a physician.
153 The mean (SD) temporal lag between stress testing and the hypertension follow-up interview
154 was 5.5 years (range: 4 – 6.8 years). Dropout between stress testing and hypertension follow-
155 up interview was 232 participants (34.6%). The study was approved by the local Medical
156 Ethics Committee, carried out in accordance with the Declaration of Helsinki, and informed
157 consent was obtained from all participants.

158 **General Study Parameters**

159 In the 2002-2004 stress testing sessions, research nurses gathered anthropometric
160 measurements and collected socioeconomic status (SES), education, and lifestyle data during
161 a standardized interview. Height was measured twice using a fixed or portable stadiometer
162 and weight was measured twice using Seca and portable Tefal scales. Body mass index
163 (BMI) was calculated as weight (kg)/height (m²) from the averages of the two height and
164 weight measures. SES was defined according to the International Socio-Economic Index
165 (ISEI)-92, which is based on the participant's or their partner's occupation, whichever has the
166 higher status¹⁸. Values on the ISEI-92 range from 16 (low status) to 87. The Hospital
167 Anxiety and Depression Scale (HADS) was used to assess anxiety and depression¹⁹.
168 Education level was measured on a 10-point scale (1 = primary education not completed, 10
169 = university completed). Alcohol consumption was recorded as the number of units

170 consumed per week; one unit was defined as one glass of an alcoholic beverage. On the basis
171 of self-report, participants were characterized as current, ex, or never smokers and also
172 indicated whether or not they were currently taking anti-hypertensive medication.

173 **Psychological Stress Protocol**

174 Stress testing was carried out in the afternoon between the hours of 12:00-14:00
175 following a light lunch. A formal 20-minute baseline was followed by three psychological
176 stress exposures: Stroop, mirror-tracing, and a speech task. Each task lasted 5 minutes and
177 was separated by 6-minute between-task intervals; a 30-minute recovery phase followed the
178 final stress task. The Stroop task was a computerised version of the classic Stroop colour-
179 word conflict task. After instruction, participants were allowed to practise until they fully
180 grasped the requirements of the task. During the task, a mistake or response over the time
181 limit (5s) triggered a beep. The mirror-tracing task required participants to trace a star that
182 could only be seen in a mirror image (Lafayette, IN, USA). Participants were allowed to
183 practice one circuit. They were told to give priority to accuracy over speed and that most
184 people could perform five circuits without diverging from the line. Every divergence from
185 the line induced a short beep. Prior to the speech task, participants listened to a pre-recorded
186 scenario in which they were told to imagine that they were falsely accused of pick-pocketing.
187 Participants were instructed to give a 3-minute response to the accusation and were given 2
188 minutes to prepare a response. The responses were recorded on video and participants were
189 told that the number of repetitions, the eloquence and the persuasiveness of their performance
190 would be marked by a team of communication-experts and psychologists.

191 Continuous measures of BP and HR were made during the stress test protocol using a
192 Finometer or Portapres Model-2 (Amsterdam, The Netherlands). There was no difference in
193 reactivity as a function of the two different measurement instruments. Four 5-minute blocks
194 were defined as follows: baseline (final 5 minutes in baseline period), Stroop, mirror-tracing,

195 and speech task (including preparation time). Mean SBP, DBP, and HR were calculated for
196 each period.

197 **Statistical Analysis**

198 Baseline SBP, DBP, and HR were the averages of measures recorded during the 5-
199 minute period 15 minutes into the formal baseline. Cardiovascular measures were averaged
200 across the three tasks to obtain a stress period average for each variable. Stress reactivity was
201 defined as the difference between stress and baseline averages for SBP, DBP, and HR. A
202 repeated-measures ANOVA, comparing baseline and stress task values, was carried out to
203 confirm that the stress tasks perturbed cardiovascular activity. **Partial eta squared and hazard**
204 **ratios are** reported as the measure of effect size.

205 Cluster analysis was carried out using Ward's method²⁰ in SPSS version 22 (Chicago,
206 IL, USA). Raw reactivity scores for SBP, DBP, and HR were converted to z-scores to ensure
207 that the cluster analysis was not influenced by the scale of individual variables. Ward's
208 method begins with the same number of clusters as cases. In each subsequent step, cases are
209 combined, forming one less cluster than before. For each cluster, a within-cluster sum of the
210 squared Euclidean distances between individual scores and the mean of each variable in that
211 cluster is calculated; the smaller the sum of squares, the greater the similarity between
212 individuals in the cluster. A total sum of squares is then calculated across all clusters.
213 Ward's method determines which two clusters will produce the smallest increase in the total
214 sum of squares when they are merged. Eventually, the merger of two dissimilar clusters will
215 cause a substantial increase in the total sum of squares. The state of the clusters just prior to
216 this point is considered the "natural solution" to the clustering process. Follow-up one-way
217 ANOVAs were carried out to determine whether clusters differed significantly on mean SBP,
218 DBP, and HR reactivity. **As data was normally distributed,** between cluster differences in
219 general study parameters were tested with one-way ANOVAs and Chi-squared analysis.

220 Binary logistic regression was used to assess whether cluster membership in 2002-2004
221 predicted reported physician diagnosis of hypertension at the 2008-2009 follow-up.
222 Following tests of unadjusted models, models were adjusted for education, SES, BMI, sex,
223 age, HADS-depression score, smoking status, and alcohol consumption, and self-reported
224 anti-hypertension medication use at stress-testing to assess the influence of potential
225 confounders.

226 Results

227 Study Population

228 Of the 740 cohort members, 721 completed the stress protocol. Cardiovascular data
229 were unavailable for four participants. Incomplete cardiovascular data due to technical
230 problems, participant exclusion, due to significant arrhythmia, determined during
231 cardiovascular data processing, and removal of two statistical outliers (> 5 standard
232 deviations above mean) left an effective sample size of 669 which is substantially above the
233 suggested sample size of 2^m needed for cluster analysis, where m is the number of clustering
234 variables²¹.

235 Stress Reactivity

236 The stress task battery significantly perturbed SBP, $F(1, 668) = 2511.21, p < .001, \eta^2$
237 $= .79$, DBP, $F(1, 689) = 579.69, p < .001, \eta^2 = .47$, and HR, $F(1, 668) = 165.48, p < .001, \eta^2$
238 $= .20$; in all cases cardiovascular activity increased in response to stress. The overall
239 magnitude of the cardiovascular perturbations is shown in Figure 1.

240 Cluster Analysis

241 Based on the criterion discussed for selecting the appropriate number of clusters, SBP,
242 DBP, and HR reactions to the stress task battery were found to resolve to four distinct
243 clusters. The means and standard errors for SBP, DBP, and HR reactivity for each cluster can
244 be found in Figure 1. Results of independent one-way ANOVAs and *post-hoc* analyses

245 showed that all the clusters were significantly different from each other on all cardiovascular
246 variables ($p < .05$) with a few exceptions: clusters 1 and 4 did not significantly differ in SBP
247 or DBP reactivity (both $p > .45$), and clusters 2 and 4 did not significantly differ in HR
248 reactivity ($p = .56$). Whereas cluster 2 was characterised by reactivity values mostly in line
249 with the sample averages, the other clusters were different in several respects. Individuals in
250 cluster 1 registered exaggerated HR and BP responses while individuals in cluster 3 exhibited
251 an overall blunted reactivity profile. Finally, individuals in cluster 4 mounted an exaggerated
252 BP response equal to that of cluster 1 but only a modest HR response statistically equal to
253 that of cluster 2.

254 Analysis of general study parameters revealed several significant differences between
255 the clusters (Table 1). Significant between-cluster differences ($p < .05$) were found for
256 education, SES, BMI, HADS-depression score, baseline DBP, gender, and smoking status.
257 There were no significant cluster differences in baseline SBP or HR, age, alcohol
258 consumption, dropout, and hypertension medication use at the time of stress testing.

259 [Insert Figure 1 about here]

260 [Insert Table 1 about here]

261 **Cluster Risk for Hypertension**

262 Hypertension status was recorded for 438 participants in 2008-2009. There was no
263 significant difference in HR or BP stress reactivity between those who participated in the
264 follow-up and those who did not. Analysis of general 2002-2004 study parameters in the
265 follow-up sample revealed significant differences between the clusters in education, SES,
266 BMI, HADS-depression score, hypertension medication use at time of stress testing, and
267 smoking status; age, gender, baseline cardiovascular variables, and alcohol consumption did
268 not significantly vary across clusters (Table 2). In all, 211 (48%) reported having received a
269 diagnosis of hypertension from a physician in the 2008-2009 follow-up. Binary logistic

270 regression confirmed a relationship between 2002-2004 cluster 4 membership and increased
271 risk of hypertension at 2008-2009 follow-up (Table 3). To assure that this relationship was
272 not influenced by those already hypertensive at the 2002-2004 stress testing session, this
273 analysis was revisited and adjustment for hypertension medication use at the time of stress
274 testing; results survived adjustment (Table 3). Finally, to explore potential mediators
275 education, SES, BMI, HADS-depression score, and smoking status were inserted as
276 covariates; cluster 4 membership was still significantly related to increased risk of
277 hypertension at follow-up (Table 3).

278 [Insert Table 2 about here]

279 [Insert Table 3 about here]

280 **Exploratory Analyses of Task Specificity**

281 Given that the current study aimed to determine if stable individual differences in
282 stress reactivity predicted individual differences in hypertension risk we chose to aggregate
283 reactivity measures across the tasks as task aggregation has been shown to result in a more
284 reliable measure of individual differences in stress reactivity²². However, we acknowledge
285 that stress tasks differ in their provoked responses and in their relevance to disease.
286 Consequently, we undertook exploratory cluster and binary logistic regression analyses for
287 each task individually. Individual cluster analyses for the speech and Stroop tasks resulted in
288 the same clusters as the main analysis and in both cases the cluster characterized by
289 exaggerated BP, but only modest HR reactivity had significantly increased risk of
290 hypertension (both HRs > 1.96 & both $p < .013$). Cluster analysis of reactivity values to the
291 mirror tracing task also revealed four distinct groups that qualitatively were similar in pattern
292 to the other tasks but cluster membership failed to predict hypertension.

293 **Discussion**

294 Using multivariate cluster analysis, four homogenous clusters of individuals with
295 statistically different SBP, DBP, and HR stress reactivity patterns were identified. Further,
296 cluster membership was found to predict increased risk of a physician diagnosis of
297 hypertension at 5 year follow-up. Interestingly, a dichotomy emerged whereby cluster 1 and
298 4 garnered the smallest and greatest risk of hypertension, respectively, despite mounting
299 statistically equal exaggerated BP stress responses; the only between-cluster difference was
300 in HR reactivity where cluster 1 mounted an exaggerated HR response and individuals in
301 cluster 4 registered small HR responses equal to the sample mean. This relationship
302 withstood adjustment for various potential anthropometric and socio-demographic
303 confounders and hypertension medication use at time of stress testing. By showing that only
304 individuals characterized by an exaggerated BP reaction and relatively small HR reaction are
305 at increased risk of hypertension, these results support, but also more specifically characterize
306 the previously reported prospective relationship between exaggerated BP reactivity and
307 hypertension. Lastly, these results critically emphasize the role of multivariate analyses in
308 stress psychophysiology research.

309 That the cluster characterized by the largest SBP and DBP stress responses had the
310 greatest risk of hypertension at 5-year follow-up was not unexpected. Moreover, this
311 relationship withstood adjustment for hypertension medication use at stress testing and
312 several potential anthropometric and socio-demographic confounders. Although mediation
313 by some other unmeasured factor is possible, it is unlikely, as previous studies have shown
314 the association between exaggerated BP stress reactivity and hypertension to withstand
315 statistical adjustment for other variables such as age, gender, and baseline BP³. What is more
316 likely is that repeated large magnitude surges in BP, induced by mental stress, engage local
317 BP regulatory mechanisms and lead over time to upward structural resetting of the peripheral
318 vasculature^{23,24}. Specifically, elevated resting BP results from a positive feedback cycle in

319 which frequent acute surges in BP promote vascular hypertrophy which decreases lumen
320 diameter and increases vessel stiffness, in turn, amplifying future BP fluctuations. Evidence
321 of such processes lies in the reported association of exaggerated BP reactivity with increased
322 carotid intima-media thickness in children²⁵, adolescents^{26,27}, and adults^{28,29}, and with
323 increased vascular stiffness³⁰ as well as the propensity for BP reactivity to increase with
324 age³¹. It is likely that such physiological processes underlie the development of hypertension
325 in the individuals contained in the cluster that displayed exaggerated BP responses to mental
326 stress¹⁻³.

327 An unexpected finding was that the cluster of individuals carrying the least risk of
328 hypertension did not have reactivity values located at the mean but instead had the most
329 exaggerated HR and BP reactions. Hence, compared to the cluster at highest risk of
330 hypertension, which had an equally exaggerated BP response but only modest cardiac
331 response, it would appear that the presence/absence of a robust HR response is, to some
332 extent, a factor in determining hypertension risk. One possible interpretation relates to the
333 early observation that similar BP reactions can result from significantly different changes in
334 cardiac output and total peripheral resistance¹². A spectrum exists in which individuals at the
335 extreme ends modulate BP by primarily augmenting either cardiac output (CO; *cardiac*
336 *reactors*) or total peripheral resistance (TPR; *vascular reactors*). Going further, it has been
337 suggested that not only is the magnitude of reactivity significant in the context of disease but
338 that different underlying mechanisms (i.e., relative degree of CO/TPR modulation) may carry
339 differential hypertension risk¹². The present results accord with this framework as the
340 individuals in the highest risk cluster registered an exaggerated BP reaction despite only a
341 modest increase in HR, whereas the cluster carrying the least amount of risk mounted an
342 equally exaggerated BP response but also recorded a HR reaction almost 3x larger than the
343 sample mean. With such differences in cardiac activity between the clusters, it may be that

344 individuals in the cluster with the least risk increased BP by augmenting cardiac output
345 through beta-adrenergic activation and/or vagal withdrawal mechanisms, while the high-risk
346 cluster increased BP primarily through alpha-adrenergic vasoconstriction^{32,33}. It is also
347 possible that the reaction patterns exhibited by individuals in clusters 2 and 3 resulted from
348 variations, not only in the degree of mixed alpha/beta -adrenergic activation, but also in
349 overall magnitude of autonomic reactivity. Hence, these data suggest that not only is the
350 magnitude with which an individual responds to mental stress significant in the context of
351 disease, but also underlying multivariate hemodynamic and autonomic mechanisms carry
352 differential risk and should be considered.

353 The current study is not without limitations. First, it could be argued that an element
354 of subjectivity exists in choosing the clustering algorithm and the final number of reactivity
355 profile clusters. These are issues with all forms of cluster analysis. We chose Ward's method
356 as it has been widely used in health psychology research³⁴ and precedence for its use exists in
357 stress psychophysiology; two previous studies have used Ward's method to cluster stress
358 reactivity patterns according to autonomic activity³³ and stress task³². Four clusters were
359 selected for two reasons: a substantial increase in total sum of squares was observed during
360 the iteration decreasing the sample from five clusters to four, and outputs with five or three
361 clusters either had very small clusters with extreme individuals or large, heterogeneous
362 clusters, respectively. Second, the effect sizes in in the current study are small. However,
363 they are consistent in magnitude with those observed in other studies³, and this is not
364 unexpected as hypertension is multiply determined, having etiological roots in the vascular,
365 autonomic, genetic, and metabolic domains³⁵. Finally, the possibility exists that famine
366 exposure *in utero* could influence the present results and limit generalizability. However, chi
367 square analysis revealed that famine exposure did not differ across the clusters ($p = .25$) nor
368 did it relate to hypertension diagnosis ($p = .17$).

369 In conclusion, using multivariate cluster analysis, four distinct HR and BP reactions
370 patterns were identified that differed in relative risk of hypertension diagnosis at 5 year
371 follow-up. A profile characterized by exaggerated BP but only modest HR reactivity
372 conferred the greatest risk, while individuals mounting relatively exaggerated BP and HR
373 responses carried the least amount of risk. These results support, but more importantly, add
374 specificity to the established relationship between blood pressure stress responses and
375 hypertension and provide positive reinforcement for the use of multivariate statistical
376 approaches in psychophysiology research.

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- 411 1. Matthews KA, Woodall KL, Allen MT. Cardiovascular reactivity to stress predicts
412 future blood pressure status. *Hypertension* 1993; **22**: 479-485.
- 413 2. Carroll D, Phillips AC, Der G, Hunt K, Benzeval M. Blood pressure reactions to acute
414 mental stress and future blood pressure status: data from the 12-year follow-up of the
415 West of Scotland study. *Psychosom Med* 2011; **73**: 737-742.
- 416 3. Matthews KA, Katholi CR, McCreath H, Whooley MA, Williams DR, Zhu S, et al.
417 Blood pressure reactivity to psychological stress predicts hypertension in the
418 CARDIA study. *Circulation* 2004; **110**: 74-78.
- 419 4. Tuomisto M. Intra-arterial blood pressure and heart rate reactivity to behavioral stress
420 in normotensive, borderline, and mild hypertensive men. *Health Psychol* 1997; **16**:
421 554-565.
- 422 5. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are
423 associated with poor subsequent cardiovascular risk status: a meta-analysis of
424 prospective evidence. *Hypertension* 2010; **55**: 1026-1032.
- 425 6. Hastrup JL, Light KC, Obrist PA. Parental hypertension and cardiovascular responses
426 to stress in healthy young adults. *Psychophysiology* 1982; **19**: 615-622.
- 427 7. von Eiff AW, Gogolin E, Jacobs U, Neus H. Heart rate reactivity under mental stress
428 as a predictor of blood pressure development in children. *J Hypertens* 1985; **3**: S89-
429 S91.
- 430 8. Vrijkotte TGM, van Doornen LJP, de Geus EJC. Effects of work stress on ambulatory
431 blood pressure, heart rate, and heart rate variability. *Hypertension* 2000; **35**: 880-886.
- 432 9. Carroll D, Phillips AC, Der G. Body mass index, abdominal adiposity, obesity, and
433 cardiovascular reactions to psychological stress in a large community sample.
434 *Psychosom Med* 2008; **70**: 653-660.

- 435 10. Ginty AT, Jones A, Carroll D, Roseboom TJ, Phillips AC, Painter R, et al.
436 Neuroendocrine and cardiovascular reactions to acute psychological stress are
437 attenuated in smokers. *Psychoneuroendocrino* 2014; **48**: 87-97.
- 438 11. Panknin TL, Dickensheets SL, Nixon SJ, Lovallo WR. Attenuated heart rate
439 responses to public speaking in individuals with alcohol dependence. *Alcohol Clin*
440 *Exp Res* 2002; **26**: 841-847.
- 441 12. Manuck SB. Cardiovascular reactivity in cardiovascular disease: "Once more unto the
442 breach." *Int J Behav Med* 1994; **1**: 4-31.
- 443 13. Klabunde RE. *Cardiovascular Physiology Concepts*. Lippincott Williams & Wilkins:
444 New York, New York, 2005.
- 445 14. Roseboom TJ, van der Meulen JHP, Ravelli ACJ, Osmond C, Barker DJP, Bleker OP.
446 Effects of prenatal exposure to the Dutch famine on adult disease in later life: An
447 overview. *Molecular and Cellular Endocrinology* 2001; **185**: 93-98.
- 448 15. Roseboom TJ, Painter RC, van Abeelen AFM, Veenendaal MVE, de Rooij SR.
449 Hungry in the womb: What are the consequences? Lessons from the Dutch famine.
450 *Maturitas* 2011; **70**: 141-145.
- 451 16. Painter RC, Roseboom TJ, Bossuyt PM, Osmond C, Barker DJ, Bleker OP. Adult
452 mortality at age 57 after prenatal exposure to the Dutch famine. *Eur J Epidemiol*
453 2005; **20**: 673-679.
- 454 17. Ravelli ACJ, van der Meulen JHP, Michels RPJ, Osmond C, Berker DJP, Hales CN,
455 et al. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998; **351**:
456 173-177.
- 457 18. Bakker B, Seiben I. Maten voor prestige, social-economische status en sociale klasse
458 voor de standard beroepenclassificatie. *Soc Wetenschap* 1992; **40**: 1-22.

- 459 19. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiat*
460 *Scandinavica* 1983; **67**: 361-370.
- 461 20. Ward JH. Hierarchical grouping to optimise an objective function. *J Am Stat Assoc*
462 1963; **58**: 236-244.
- 463 21. Mooi E, Sarstedt M. Cluster Analysis. In: Mooi E, Sarstedt M. (eds). *A Concise Guide*
464 *to Market Research*, 1st edn. Springer-Verlag Berlin Heidelberg: Berlin, Heidelberg,
465 Germany, 2011, pp 243.
- 466 22. Kamarck TW, Jennings JR, Manuck SB. Psychometric applications in the assessment
467 of cardiovascular reactivity. *Homeostasis Hlth Dis* 1992; **34**: 229-243.
- 468 23. Folkow B. "Structural factors" in primary and secondary hypertension. *Hypertension*
469 1990; **16**: 89-101.
- 470 24. Obrist P. *Cardiovascular Psychophysiology: A perspective*. Plenum Press: New York,
471 New York, 1981.
- 472 25. Roemmich JN, Lobarinas CL, Joseph PN, Lambiase MJ, Archer III FD, Dorn J.
473 Cardiovascular reactivity to psychological stress and carotid intima-media thickness
474 in children. *Psychophysiology* 2009; **46**: 293-299.
- 475 26. Lambiase MJ, Dorn J, Roemmich JN. Metabolic and cardiovascular adjustments
476 during psychological stress and carotid artery intima-media thickness in youth.
477 *Physiol Behav* 2012; **105**: 1140-1147.
- 478 27. Roemmich J, Feda DM, Seelbinder AM, Lambiase MJ, Kala GK, Dorn J. Stress-
479 induced cardiovascular reactivity and atherogenesis in adolescents. *Atherosclerosis*
480 2011; **215**: 465-470.
- 481 28. Jennings JR, Kamarck TW, Everson-Rose SA, Kaplan GA, Manuck SB, Salonen JT.
482 Exaggerated blood pressure responses during mental stress are prospectively related

- 483 to enhanced carotid atherosclerosis in middle-aged Finnish men. *Circulation* 2004;
484 **110**: 2198-2203.
- 485 29. Kamarck TW, Everson SA, Kaplan GA, Manuch SB, Jennings JR, Salonen R, et al.
486 Exaggerated blood pressure responses during mental stress are associated with
487 enhanced carotid atherosclerosis in middle-aged Finnish men. *Circulation* 1997; **96**:
488 3842-3848.
- 489 30. Lipman RD, Grossman P, Bridges SE, Hamner JW, Taylor JA. Mental stress
490 responses, arterial stiffness, and baroreflex sensitivity in healthy aging. *J Gerontol*
491 *Biol Sci* 2002; **57**: B279-B284.
- 492 31. Uchino BN, Birmingham W, Berg CA. Are older adults less or more physiologically
493 reactivity? A meta-analysis of age-related differences in cardiovascular reactivity to
494 laboratory tasks. *J Gerontol Psychol Sci* 2010; **65B**: 154-162.
- 495 32. Allen MT, Boquet AJ, Shelley, KS. Cluster analysis and cardiovascular responsivity
496 to three laboratory stressors. *Psychosom Med* 1991; **53**: 272-288.
- 497 33. Mills PJ, Dimsdale JE, Nelesen RA, Jasiewicz J, Ziegler MG, Kennedy B. Patterns of
498 adrenergic receptors and adrenergic agonists underlying cardiovascular responses to a
499 psychological challenge. *Psychosom Med* 1994; **56**: 70-76.
- 500 34. Clatworthy J, Buick D, Hankins M, Weinman J, Horne R. The use and reporting of
501 cluster analysis in health psychology. *Brit J Health Psych* 2005; **10**: 329-358.
- 502 35. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. *Ann Intern Med*
503 2003; **139**: 761-776.

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507 **Figure 1.** Means of systolic (SBP), diastolic (DBP), and heart rate (HR) reactivity in mmHg
508 or beats per minute for overall sample and individual clusters. HR reactivity is significantly
509 different across all clusters, with the exception of clusters 2 and 4. SBP and DBP reactivity is
510 significantly different across clusters with the exception of clusters 1 and 4. Error bars
511 represent standard error.

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Summary Table

What is known about the topic

- Exaggerated blood pressure reactions to acute psychological stress are associated with increased risk of hypertension
- Links between exaggerated heart rate stress responses and hypertension are inconsistent and blunted heart rate stress reactions have been linked to hypertension risk factors (e.g., obesity, smoking, heavy alcohol consumption). This creates a paradox since heart rate and blood pressure stress reactions are not mutually exclusive, but are linked through cardiovascular regulatory mechanisms.
- Multivariate patterns of heart rate and blood pressure stress reactivity have been seldom explored with regard to disease risk.

What this study adds

- Using multivariate cluster analysis, four unique clusters of individuals were identified that statistically differed in the magnitude of heart rate and blood pressure reactivity to a battery of mental stress tasks.
- The cluster with the least amount of risk mounted a relatively exaggerated heart rate and blood pressure response while the cluster with the greatest risk mounted an exaggerated blood pressure, but relatively small heart rate response.
- This study adds specificity to the already established link between blood pressure stress reactivity and hypertension and reinforces the use of multivariate approaches to stress psychophysiology.

Table 1: General Study Parameters of Clusters 2002-2004 Wave (N = 669)

	Cluster 1 (N = 85)	Cluster 2 (N = 268)	Cluster 3 (N = 184)	Cluster 4 (N = 132)
Education	5.2 (2.3)†	4.5 (2.1)	4.1 (2.2)*	4.7 (2.2)
SES	55.0(11.8)# †‡	49.9 (14.2)*	47.3 (14.3)*	49.8 (14.0)*
BMI (kg/m ²)	26.8 (3.6)#† ‡	28.5 (4.6)*†	29.4 (5.2)*#	29.2 (4.6)*
HADS-Depression	2.3(2.3) †	3.3 (3.2)	3.8 (3.0)* ‡	2.8 (2.7)†
Smoking (% smokers) ^a	7.1	22.8	38.3	15.2
Hypertension Medication Use ^b	15.3%	17.9%	26.1%	33.3%
Sex (% female) ^a	50.6%	46.6%	60.3%	53.0%
Age	58.5 (1.0)	58.2 (0.9)	58.3 (1.0)	58.2 (0.9)
Alcohol	10.5 (11.6)	10.0 (14.2)	8.9 (12.9)	10.1 (15.1)
Dropout ^c	32.9%	35.8%	37.0%	29.5%
Baseline SBP	133.2 (22.3)	127.3 (19.9)	127.7 (20.2)	126.9 (21.8)
Baseline DBP	70.3 (11.6)# ‡	66.0 (11.0)*	67.2 (12.1)	65.2 (13.9)*
Baseline HR	75.4 (10.1)	73.4 (10.2)	74.7 (11.0)	73.3 (10.8)

Note: Values are reported as Mean (SD). *different from Cluster 1, #different from Cluster 2, †different from Cluster 3, ‡different from Cluster 4

^a denotes significant Chi-Square ($p < .05$)

^b denotes those reporting medication usage

^c denote percent not returning in 2008-2009

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Table 2: General Study Parameters of Clusters 2008-2009 Wave (N = 438)

	Cluster 1 (N = 57)	Cluster 2 (N = 172)	Cluster 3 (N = 116)	Cluster 4 (N = 93)
Education	5.3 (2.2)†	4.6 (2.1)†	3.9 (1.9)*#	4.6 (2.1)
SES	54.7 (11.2)†	51.2 (14.0)	47.0 (13.7)*	50.3 (14.0)
BMI (kg/m ²)	26.9 (3.2)#†‡	28.5 (4.7)*	29.3 (5.2)*	29.2 (4.5)*
HADS-Depression	2.1 (1.8) †	3.2 (3.3)	3.6 (2.9)*	2.7 (2.8)
Smoking (% smokers) ^a	5.3	23.8	36.5	15.1
Hypertension Medication Use ^{ab}	12.3%	18.0%	30.2%	33.3%
Sex (% female)	52.6%	47.7%	58.6%	53.8%
Age	58.5 (1.0)	58.2 (0.9)	58.2 (0.9)	58.1 (0.9)
Alcohol	9.9 (9.4)	10.3 (15.9)	9.7 (14.4)	8.7 (15.6)
Baseline SBP	132.6 (20.1)	127.1 (19.7)	127.4 (19.4)	127.4 (20.1)
Baseline DBP	70.0 (10.7)	66.4 (11.2)	67.4 (12.7)	66.4 (11.9)
Baseline HR	75.8 (9.5)	73.8 (10.0)	74.2 (10.7)	74.4 (10.1)

Note: Values are reported as Mean (SD). Differences denote p <.05 *different from Cluster 1, #different from Cluster 2, †different from Cluster 3, ‡different from Cluster 4

^a denotes significant Chi-Square (p <.05)

^b denotes those reporting medication usage

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Table 3: Hazard Ratio of Physician Diagnosis of Hypertension by Stress Reactivity Cluster

Reactivity Clusters	HR ^a (95% CI), <i>p</i> Value	HR ^b (95% CI), <i>p</i> Value	HR ^c (95% CI), <i>p</i> Value
Cluster 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cluster 2	1.23 (0.66-2.29), 0.50	1.11 (0.57-2.15), 0.77	0.88 (0.45-1.73), 0.70
Cluster 3	1.71 (0.90-3.28), 0.10	1.22 (0.60-2.48), 0.59	1.17 (0.56-2.47), 0.68
Cluster 4	2.98 (1.50-5.90), <.01	2.24 (1.07-4.69), 0.03	2.17 (1.04-4.55), 0.04

^aHR, unadjusted

^bHR, adjusted for hypertension medication at stress testing phase 2002-2004

^cHR, adjusted for education, SES, BMI, HADS-depression score, and smoking status

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