Cardiovascular reactivity patterns and pathways to hypertension: a multivariate cluster analysis

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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

Introduction

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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-up[1-2] and to predict hypertension diagnosis at 13-year

101   follow-up[3]. In addition, being "high risk" for developing hypertension based on parental

102   history or having elevated resting BP are associated with exaggerated BP stress reactivity[4].

103   Importantly, a large meta-analysis also has established a positive association between BP

104   stress reactivity and hypertension[5].

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 hypertension[6] and several small scale studies have

108   reported a positive association between HR stress reactivity and increased 1-year ambulatory

109   SBP[7] and incident mild hypertension[8]. However, a relationship between HR reactivity and

110   elevated BP has failed to emerge from epidemiological studies[3] or meta-analysis[5]. 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 obese[9], smokers[10], and those dependent on alcohol[11] 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 disease[12] and that focusing on multivariate patterns of stress

120 reactivity may be more informative[12]. 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 mechanisms[13].

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 calories[14] (Roseboom, van der Meulen,

139 Raveli, Osmond, Barker, & Bleker, 2001), was associated with poorer adult health[15]

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 ($\text{mean}_{refused} = 58.3\text{yrs}$,

150 $\text{mean}_{attended} = 59.2\text{yrs}$, $p < .01$).

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 (m^2) 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 status[18]. 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 depression[19].

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.

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 method[20] 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   variables[21].

235   **Stress Reactivity**

236   The stress task battery significantly perturbed SBP, $F(1, 668) = 2511.21$, $p < .001$, η^2

237     $= .79$, DBP, $F(1, 689) = 579.69$, $p < .001$, $\eta^2 = .47$, and HR, $F(1, 668) = 165.48$, $p < .001$, η^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 reactivity[22]. 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 predicted 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 BP[3]. 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 children[25], adolescents[26,27], and adults[28,29], and with

323   increased vascular stiffness[30] as well as the propensity for BP reactivity to increase with

324   age[31]. 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   stress[1-3].

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 resistance[12]. A spectrum exists in which individuals at the

335   extreme ends modulate BP by primarily augmenting either cardiac output (CO; *cardiac*

336   *reactor*s) or total peripheral resistance (TPR; *vascular reactor*s). 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 risk[12]. 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 research[34] 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 activity[33] and stress task[32]. 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 studies[3], and this is not

364   unexpected as hypertension is multiply determined, having etiological roots in the vascular,

365   autonomic, genetic, and metabolic domains[35]. 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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390   **Acknowledgments**

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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 expectation 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.

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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)	7.4 (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), *p* Value	HR[b] (95% CI), *p* Value	HR[c] (95% CI), *p* 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

[a]HR, unadjusted

[b]HR, adjusted for hypertension medication at stress testing phase 2002-2004

[c]HR, adjusted for education, SES, BMI, HADS-depression score, and smoking status

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