Diminished heart rate reactivity to acute psychological stress is associated with enhanced carotid intima-media thickness through adverse health behaviors.

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Running head: Heart rate reactivity and intima-media thickness

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Abstract

Recent evidence demonstrates that individuals with low heart rate (HR) reactions to acute psychological stress are more likely to be obese or smokers. Smoking and obesity are established risk factors for increased carotid intima-media thickness (IMT). The aim of this study was to examine the potential pathways linking intima-media thickness (IMT), smoking, body mass index (BMI), and HR stress reactivity. 552 participants (47.6% male, M (SD) age = 58.3 (0.94) years) were exposed to three psychological stress tasks (Stroop, mirror drawing, and speech) preceded by a resting baseline period; HR was recorded throughout. HR reactivity was calculated as the average response across the three tasks minus average baseline HR. Smoking status, BMI, and IMT were determined by trained personnel. Controlling for important covariates (e.g., SES), structural equation modelling revealed that BMI and smoking mediated the negative relationship between HR reactivity and IMT. The hypothesized model demonstrated a good overall fit to the data [$\chi^2(8) = 0.692$, p = .403; CFI = 1.00; TLI = 1.00 SRMR = .01; RMSEA < .001 (90% CI < 0.01 – 0.11)]. HR reactivity was negatively related to BMI (β = -.16) and smoking (β = -.18) and these in turn were positively associated with IMT (BMI: β = .10; smoking: β = .17). Diminished HR stress reactivity appears to be a marker for enlarged IMT and appears to be exerting its impact through already established risks. Future research should examine this relationship longitudinally and aim to intervene early.

Keywords: Heart rate reactivity, stress, body mass index, smoking, intima-media thickness

Cardiovascular disease (CVD) is the cause of over 610,000 deaths in the US annually (CDC, 2015) and accounts for 46% of all deaths in Europe (Nichols, Townsend, Scarborough, & Rayner, 2014). Intima-media thickness (IMT) is a well-established measure of subclinical atherosclerosis and a robust predictor of future vascular events (Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007; Lorenz, von Kegler, Steinmetz, Markus, & Sitzer, 2006). IMT predicts CVD mortality and all-cause mortality, stroke, and future clinical coronary events (Chaves et al., 2004; Kuller et al., 1995). There is also substantial evidence that potentially modifiable behaviors such as diet, smoking, and exercise are associated with future CVD (Control, 2011; Houterman et al., 2002). To best prevent CVD it is essential to identify risk markers of unhealthy behaviors associated with both CVD and subclinical markers such as IMT.

Diminished HR reactivity has been cross-sectionally associated with larger plaque area (Barnett, Spence, Manuck, & Jennings, 1997) and greater IMT (Chumaeva et al., 2009; Kamarck et al., 1997). Although there are studies reporting no relationship between diminished HR reactivity and markers of CVD (Jennings et al., 2004; Matthews et al., 1998), longitudinal relationships between diminished HR reactivity and both coronary artery calcification (Matthews, Zhu, Tucker, & Whooley, 2006) and greater IMT (Heponiemi et al., 2007) have also been observed. However, in the studies with null results, behavioral risk factors associated with both CVD and diminished HR reactivity were controlled for in the final analyses, eliminating the significance of any association between diminished HR reactivity and markers of CVD (Matthews et al., 2006). Obesity and cigarette smoking are two such risk factors (e.g., (Khan et al., 2011; Polak et al., 2010). Those who exhibit diminished physiological responses to acute psychological stress are

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more likely to be obese and to be smokers (Carroll, Phillips, & Der, 2008; Evans et al., 2012; A.T. Ginty et al., 2014; Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997; A.C. Phillips, Roseboom, Carroll, & de Rooij, 2012; Roy, Steptoe, & Kirschbaum, 1994; Sheffield, Smith, Carroll, Shipley, & Marmot, 1997; Singh & Shen, 2013). Longitudinal research shows that diminished stress reactivity predicts the likelihood of becoming obese (Carroll et al., 2008); Phillips, Roseboom, Carroll, & de Rooij, 2012) and also of relapsing after smoking cessation (al'Absi, 2006; al'Absi, Hatsukami, & Davis, 2005; A.C. Phillips et al., 2012). Consequently, diminished stress reactivity may put individuals at risk for CVD through its association with established risk factors such as obesity and smoking.

The relationship between HR stress reactivity, risk factors such as smoking and high BMI, and the risk of cardiovascular disease remains unclear. The aim of the present study was to examine the potential pathways linking IMT, smoking, BMI, and HR reactivity. Based on the associations between HR stress reactivity and behavioral risk factors, and the associations between HR reactivity and IMT, it was hypothesized that HR reactivity would be negatively associated with smoking and a high BMI, which in turn would be positively associated with an enlarged IMT. Consequently, it was hypothesized that smoking and BMI would mediate the relationship between HR reactivity and IMT. The hypothesized model and two alternate models are displayed in Figure 1.

Method

Participants

Participants were selected from the Dutch Famine Birth Cohort Study which consists of 2414 men and women who were born in Amsterdam, the Netherlands, between

November 1943 and February 1947. Exclusion criteria for the Dutch Famine Birth Cohort study included: missing main medical records and gestational age at birth less than 259 days. Participants were identified from the Gemeentearchief (city archive). They were then traced from the Bevolkingsregister (population registry) of Amsterdam and invited to take part in the study (Ravelli et al., 1998; Painter et al., 2005). 1423 members of the cohort whose current address was known were invited to a clinic to receive a detailed medical examination, including stress testing; a total of 740 attended and 721 completed the stress testing. Logistical problems (n = 5) and illness (n = 10) prevented some participants from finishing the stress protocol. Due to technical problems, HR recordings were unavailable for four individuals. Incomplete cardiovascular data (n = 42) or IMT data (n = 112) resulted in a total available sample of 552 participants. There were no exclusion criteria. The study was approved by the local Medical Ethics Committee and carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent.

General Study Parameters

Participants arrived at the hospital at 0800 hours after an overnight fast. They were not given sleep or smoking instructions prior to their visit. After completing consent forms, trained research nurses took anthropometric measurements and conducted a standardized interview in which information was obtained about socio-economic status (SES), lifestyle and the use of medication. Height was measured twice using a fixed or portable stadiometer and weight twice using Seca and portable Tefal scales. Body Mass Index (BMI) was computed as weight (kg)/height (m^2) from the averages of the two height and weight measurements. During the interview participants were asked "Do you

currently smoke cigarettes?" They were given the option of answering "Yes, on average 1 or more cigarettes per month," "Yes, but on average less than 1 cigarette per month," "No, I used to smoke cigarettes, but now I don't anymore," and "No, I never smoked." There were no participants who answered "Yes, but on average less than 1 cigarette per month." Therefore, smoking status was divided into a three category variable: current, ex-, or never smokers. Participants were asked at what age they began smoking (current and ex-smokers) and at what age they quit (ex-smokers). Additionally, current smokers were asked how many cigarettes per day they smoked. SES was defined according to the participant's or their partner's occupation, whichever had the higher status (Bakker & Sieben, 1997). Values in the ISEI-92 scale ranged from 16 (low status) to 87. Participants were also asked to indicate if they had ever received a diagnosis of hypertension from a physician.

Psychological Stress Protocol

The stress protocol started in the afternoon between the hours of 12:00 and 14:00 on the day participants visited the clinic, approximately an hour after a light lunch. It began with a 20-min baseline period, after which three psychological stress tasks were undertaken in a fixed order: Stroop, mirror tracing, and speech tasks. Participants remained in a seated position during all phases. Each task lasted 5 minutes with 6 minute intertask intervals. The Stroop task consisted of a single-trial computerized version of the classic Stroop color-word conflict challenge. Errors and exceeding the response time limit of 5 s triggered a short auditory beep. For the mirror-tracing task, a star had to be traced that could only be seen in a mirror image (Lafayette Instruments Corp., Lafayette, IN, USA). Every divergence from the line triggered an auditory stimulus. Prior to the speech

task, participants listened to an audio tape instruction in which they were told to imagine a situation in which they were falsely accused of pick pocketing. They were then given 2 min to prepare a 3 min speech in which they had to respond to the accusation.

Continuous HR measurements were made using a Finometer or a Portapres Model -2 (Finapres Medical Systems, Amsterdam, The Netherlands). There were no differences in reactivity as a function of the two different medical devices. Four periods of 5 min were designated as the key measurement periods: resting baseline (15 min into the baseline period), Stroop, mirror-tracing task, and speech task (including preparation time). Mean HR was calculated for each measurement period. HR reactivity was calculated as the difference between the average of the three task means minus the average of the three baseline means. Using an average of multiple stress tasks has been shown to increase reliability (Kamarck, Jennings, & Manuck, 1993) and is common practice (e.g., Yano et al., 2016).

Intima-Media Thickness Measurement

B-mode ultrasound examinations of the arterial walls of the common, bulb and internal carotid artery segments, and the common and superficial femoral artery segments were undertaken. Two trained investigators (RCP and SdR) carried out the majority (92%) of the ultrasound examinations. Four other experienced sonographers carried out the remainder. The ultrasound was performed using an Acuson 128XP/10v (Acuson Corp, Mountain view, Calif) ultrasound instrument equipped with a 5-10 MHz L7 (Acuson L7) and Extended Frequency software, version 7.02 (Acuson Corp). The left and right far-walls of the carotid and femoral artery segments were imaged in standardized magnification (Regional Expansion Selection 2 x 2 cm). Vessel lumen diameter was

measured in the distal common carotid artery only. The sonographer saved stills of the B-mode images as 4:1 compressed JPEG files (Sony DKR-700P video still image recorder). Once data were collected, two image analysts batch-read all ultrasound images. They were blind to the identity of the participant. In-house designed software for image analysis (eTrack, version 2.3, W.J. Stok, Dept of Physiology, AMC, University of Amsterdam) was used (de Groot et al., 1998).

Mean carotid IMT was defined as the mean IMT in mm of the right and left common artery, carotid bulb, and the internal carotid far wall segments. If either the right or left value was missing for any given carotid segment, the remaining available segment was used to calculate the mean carotid IMT. If both right- and left-sided values were missing for any given carotid segment, the mean carotid was coded as missing. Mean femoral artery IMT was defined as the mean of the right and left common femoral artery and the right and left superficial femoral artery. The same procedure applied for missing measurements of the femoral artery.

The arterial lumen was defined as the distance between the contours of the near wall intima-lumen and the far wall lumen-intima interfaces as traced by automated contour detection software (eTrack, version 2.3, W.J. Stok, Dept of Physiology, AMC, University of Amsterdam). The mean distal common carotid lumen diameter was calculated by averaging the distance between the near and far wall interfaces for at least two heartbeats. The mean of left and right carotid diameter measurements was calculated. If either of these were missing, the carotid diameter measurement of the remaining side was used.

Data Analysis

Data were analyzed using the computer packages IBM SPSS 20.0 and AMOS 16.0. First, a repeated measure ANOVA determined whether the acute psychological stress tasks significantly perturbed HR. A one-way ANOVA examined variations in HR reactivity with smoking status and bivariate correlations determined the associations between HR reactivity and BMI. Regression analysis then examined whether HR reactivity was associated with IMT thickness before path analysis examined whether smoking and BMI mediated this relationship.

The path analysis model goodness of fit was tested using the chi-squared likelihood statistic ratio (χ^2; (Joreskog & Sorbom, 1993)). Since a non-significant value is rarely obtained in practice, additional fit indices based on Hu and Bentler's (Hu & Bentler, 1999) recommendations were also employed. The standardized root mean square residual (SRMR; (Bentler, 1995) and Root Mean Square Error of Approximation (RMSEA) indicated absolute fit (values of $\leq$ .08 and .06 respectively representing an adequate fit; (Hu & Bentler, 1999). The Tucker Lewis Index (TLI) and Comparative Fit Index (CFI) reflected incremental fit (values > .90 and > .95 indicating an adequate and excellent model fit respectively; (Hu & Bentler, 1999).

Mediation analysis was conducted following Hayes' (Hayes, 2013) recommendation of testing for indirect effects. This involved testing the indirect effects of HR reactivity on smoking and BMI (i.e., the mediators) to examine whether they were indirectly associated with IMT. Bootstrapping of 2000 samples was used to generate 90% confidence intervals. Standardized regressions and 90% confidence intervals were reported for significant indirect effects.

Finally, the fit of the hypothesized model was compared to two alternative models to determine whether the relationship between HR reactivity and IMT being mediated by smoking and BMI provided the best fit to the data. The first alternate model examined whether smoking and BMI were associated with HR reactivity which in turn was associated with IMT, and the second alternate model examined whether smoking and BMI were associated with IMT which in turn was associated with HR reactivity. The same fit indices as those employed when testing the hypothesized model were employed. To control for SES, famine exposure, sex, resting HR, and diagnosis of hypertension/taking antihypertensive medication, these variables were entered into all models.

Sensitivity analyses were conducted to examine the association in ex-smokers with how recently they quit smoking and how many years they smoked with the main study variables (HR reactivity, IMT). Additional correlation analyses were run to examine the association between lifetime smoking exposure, number of cigarettes per day/20 x years smoked (= pack years), in current and ex-smokers. The fully-adjusted model was run using reactivity to the speech task, rather than average reactivity.

Results

Cardiovascular reactions to acute psychological stress

A repeated-measures ANOVA demonstrated that stress exposure significantly perturbed the cardiovascular system, $F(4,1653) = 480.67$, $p < .001$, $\eta^2 = .466$. Post-hoc analyses indicated that each condition (baseline, stroop, mirror, speech) was different from all other conditions. Examination of means showed that heart rate increased with each stress task and was therefore highest during the final stress task, the speech task. As

previously noted, HR reactivity was calculated as the difference between the average of the three tasks means minus the average of the three baseline means. Mean reactivity, standard deviations, and range of values for each individual stress task and the average of all three tasks are reported in Table 1.

Descriptive Characteristics

Descriptive characteristic means, standard deviations and range of scores are depicted in Table 1. A one-way ANOVA demonstrated that HR reactivity was significantly different between the smoking categories. Post hoc analysis indicated that the smokers ($M = 4.35$, $SD = 5.02$) had significantly lower heart rate reactivity than the ex-smokers ($M = 6.74$, $SD = 6.84$) and those who had never smoked ($M = 7.75$, $SD = 6.47$). Correlation analysis revealed that HR reactivity correlated negatively with BMI ($r = -.18$, $p < .001$) and IMT ($r = -.11$, $p = .008$), and BMI correlated positively with IMT ($r = .15$, $p < .001$).

Hypothesized Model

First, HR reactivity was negatively associated with IMT ($\beta = -.11$, $p = .007$). Next, smoking and BMI were entered into the model as potential mediators of this association and regression paths were added from HR reactivity to both smoking and BMI and from smoking and BMI to IMT. Famine exposure, SES, sex, resting HR, and diagnosis of hypertension/taking antihypertensive medication were entered as covariates. The results revealed an excellent fit to the data, $\chi^2 (1) = 0.692$, $p = .403$, CFI $= 1.00$, TLI $= 1.00$, SRMR $= .01$, RMSEA $< .001$ (90% CI $= < 0.01$ to 0.11). Regarding the control variables, BMI was significantly predicted by resting HR ($\beta = .10$, $p = .013$) and diagnosis of hypertension ($\beta = .28$, $p < .001$), smoking was significantly predicted by SES ($\beta = -.18$,

$p < .001$) and diagnosis of hypertension ($\beta = -.10$, $p = .012$), and IMT was significantly predicted by sex ($\beta = -.16$, $p < .001$), and diagnosis of hypertension ($\beta = -.11$, $p = .007$). HR reactivity was negatively associated with smoking ($\beta = -.18$, $p < .001$) and BMI ($\beta = -.16$, $p < .001$). In turn, smoking ($\beta = .17$, $p < .001$) and BMI ($\beta = .10$, $p = .019$) were positively associated with IMT. However, the direct path from heart rate reactivity to IMT became non-significant ($\beta = -.07$, $p = .096$). This model is displayed in Figure 2 with standardized regression weights.

Although HR reactivity did not directly relate to IMT when accounting for smoking and BMI, there was an indirect pathway via smoking and BMI ($\beta = -.05$, $p = .001$, CI = -.072 to -.030). This suggests the relationship between HR reactivity and IMT is mediated by both smoking and BMI.

[Insert Figures about here]

Alternate Models

To ensure the hypothesized model demonstrated the best fit to the data, two alternate models were tested. For the first alternate model, regression paths were drawn from smoking and BMI to HR reactivity, and from HR reactivity to IMT. Our results provided a poor fit to this model, χ^2 (2) = 21.35, $p < .001$, CFI = .87, TLI = -.77, SRMR = .03, RMSEA = .13 (90% CI = 0.09 to 0.19). The second alternate model entered regression paths from smoking and BMI to IMT, and from IMT to reactivity. The results provided an even poorer fit to the model, χ^2 (2) = 30.12, $p < .001$, CFI = .82, TLI = -2.27, SRMR = .03, RMSEA = .16 (90% CI = 0.11 to 0.21). In sum, the hypothesized

model emerges as the most appropriate model for explaining the relationship between HR reactivity and IMT.

Sensitivity Analyses

There was no association among ex-smokers between number of years smoked or how recently they quit with either HR reactivity or IMT (p's > .11). Previous research from this dataset demonstrates that lifetime exposure to smoking, number of pack years, is not associated with HR reactivity (Ginty et al., 2014). Additional analyses demonstrate that lifetime exposure to smoking is not related to IMT (p's > .65). Sensitivity analyses re-running the final model, described above, using reactivity to the speech task rather than average reactivity produced virtually identical results (χ^2 (1) = 0.405, p = .525, CFI = 1.00, TLI = 1.15, SRMR = .01, RMSEA < .001 (90% CI = < 0.01 to 0.10).

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Discussion

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This is the first study to show that diminished HR reactivity is associated with increased risk of cardiovascular disease, measured as IMT, but through the former's association with smoking and high BMI. In a series of structural equation models it was shown that low HR reactivity is associated with an increased likelihood of being a smoker and of being obese and that these in turn were associated with greater IMT. Alternative models examining whether smoking and obesity related to lower HR reactivity which, in turn, was associated with IMT, or if smoking and obesity were related to IMT which, in turn, was associated with lower HR reactivity failed to offer a good fit to the data.

The present results are in line with previous cross-sectional research suggesting a negative association between HR stress reactivity and IMT (Kamarck et al., 1997). However, most of the previous research has focused on the associations between larger

amplitude blood pressure stress reactions and IMT. Exaggerated blood pressure reactions

to acute psychological stress have been associated with greater IMT both cross-sectionally

(Kamarck et al., 1997; Lambiase, Dorn, & Roemmich, 2012) and longitudinally (Jennings

et al., 2004; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews et al., 1998).

Although not the focus of this paper, it should be noted there was also an association

between systolic blood pressure reactivity and IMT; in contrast to HR reactivity, however,

in line with previous research (Kamarck et al., 1997; Lambiase, Dorn, & Roemmich,

2012), those with higher systolic blood pressure reactivity had greater IMT after

controlling for confounding variables. Indeed exaggerated blood pressure reactivity also

predicts mortality from cardiovascular disease (Carroll et al., 2012). It was only recently

that the range of unhealthy behaviors associated with diminished HR reactivity began to

be studied extensively (A. C. Phillips, Ginty, & Hughes, 2013). Accordingly, it is not

surprising that earlier research has failed to focus on the possible links between diminished

HR reactivity and CVD, and whether it is mediated by behavioral risk factors. Some of

the associations between low reactivity and cardiovascular disease may have been

presented as null results following statistical adjustment for the behavioral risk factors

linked to low reactivity (e.g., smoking, BMI; (Matthews et al., 2006).

Many interventions aimed at reducing the risk of or preventing the progression of

CVD aim to modify unhealthy behaviors and require active participation from participants.

Diminished stress reactivity has been related to lower levels of perseverance (al'Absi et al.,

2005; A.T. Ginty, in press) For example, diminished stress reactivity has been linked to a

shorter time to relapse during a variety of cessation and/or treatment programs (al'Absi et

al., 2005; Back et al., 2010; Junghanns et al., 2003). Further, a recent study showed that

adolescents who had diminished HR reactivity were less likely to complete the follow-up portion of a study (A. T. Ginty, Brindle, & Carroll, 2015). These findings suggest that diminished HR reactivity may provide a useful prognostic marker, enabling the identification of individuals who are less likely to complete or fully engage with common multi-session behavioral intervention programs. Measuring someone's HR reactivity to an acute psychological stress task may be an inexpensive, yet informative, tool for identifying individuals who would benefit from early intervention and identifying individuals who may need extra support when enrolling in such programs.

The present study is not without limitations. It is unknown whether participants smoked in the morning, prior to the stress testing session, however, nicotine withdrawal has been shown not to relate to lower reactivity (Girdler et al., 1997). The study is cross-sectional and determining definite causality is impossible (Christenfeld, Sloan, Carroll, & Greenland, 2004). However, the use of a large sample size and SEM ensured that the hypothesized model could be directly compared to other models. The significant associations between HR reactivity, smoking and BMI, and IMT, and the goodness of fit statistics confirmed that the hypothesized model provided an excellent fit to the data, whereas alternative models afforded a poor fit. Nevertheless, future research should examine these relationships longitudinally.

It would appear that, although mediated by different mechanisms, both exaggerated and diminished cardiovascular responses to acute psychological stress are associated with increased risk for CVD. Exaggerated blood pressure reactivity may provide a direct pathway to CVD through repeated strain on the vascular system, while diminished HR reactivity may be indirectly related through its association with behavioral

risk factors. It would be of interest to examine what is the strongest predictor of CVD (i.e., is it diminished HR reactivity via behavioral risk or exaggerated blood pressure reactivity via a direct pathway). Future research should focus on the longitudinal relationship between blood pressure and HR reactivity, unhealthy behaviors, obesity and development of CVD.

Acknowledgements

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Table 1.

Participant information

		Mean (SD)/n/%	Min - Max
Age		58.32 (0.93)	55.70 - 60.62
BMI		28.61 (4.73)	18.55 - 50.35
Average HR reactivity		6.60 (6.46)	-9.84 - 34.62
Stroop HR reactivity		3.90 (5.39)	-10.65 - 35.60
Mirror HR reactivity		4.43 (6.40)	-10.76 - 29.68
Speech HR reactivity		11.47 (10.12)	-9.57 - 57.91
IMT		0.68 (0.14)	.40 - 1.28
Sex	Male	263/48%	
	Female	289/52%	
Smoking status	Smoker	119/22%	
	Ex-smokers	228/41%	
	Never smoked	205/37%	
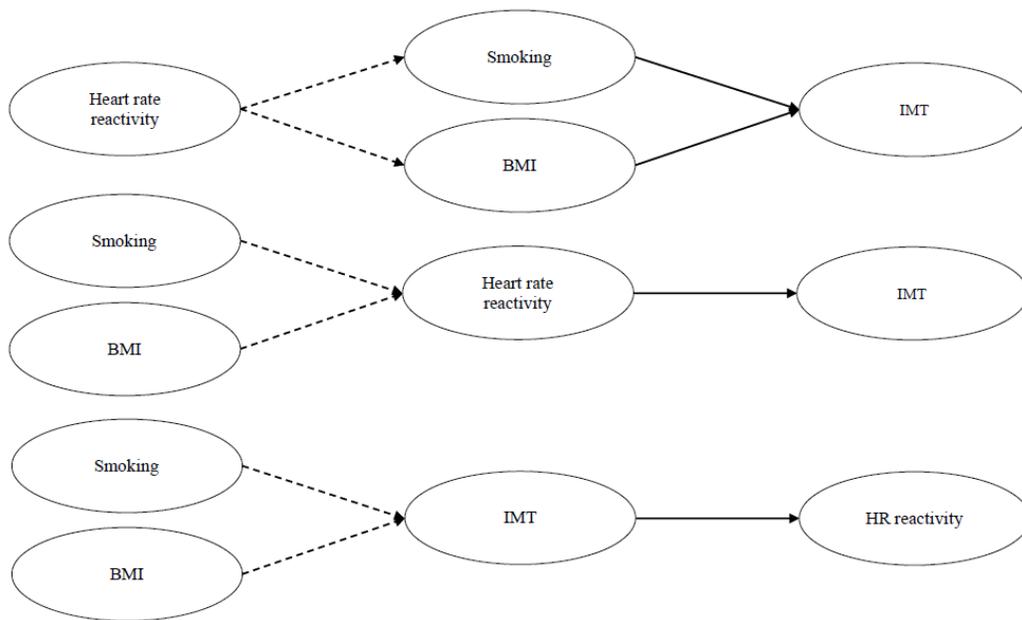
Figure 1.a. Hypothesized model. b. Alternate model 1, c. Alternate model 2. For visual simplicity, controlling variables social economic status, sex, famine exposure, diagnosis of hypertension, and resting heart rate are not presented but were controlled for in the analysis. *Note:* Full lines are positive predictions and dashed lines are negative predictions.

Figure 2. Final mediation model predicting IMT. *Note:* All coefficients are standardized. * *p* < .05, ** *p* < .001. Full lines are positive predictions and dashed lines are negative predictions. Controlling variables social economic status, sex, famine exposure, diagnosis of hypertension, and resting heart rate are not presented but were controlled for in the analysis.