Published in final edited form as:
Health Psychol. 2012 July ; 31(4): 525–529. doi:10.1037/a0025990.

Subjective Social Status predicts In Vivo Responsiveness of β-Adrenergic Receptors

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Abstract

Objective—Several poor health outcomes, including cardiovascular risk, have been associated with both subjective social status (SSS) and sympathetic over-activity. Because prolonged sympathetic over-activation down regulates beta adrenergic receptor (β-AR) function, reduced β-AR responsiveness is considered an indicator of sympathetic over-activity and a cardiovascular risk factor. While prior research has focused on objective social status and β-AR function, no studies have examined the association between SSS and β-AR function. We aimed to learn whether SSS predicts the in vivo responsiveness of β-ARs.

Methods—We assessed the Chronotropic 25 Dose (CD_{25}), an in-vivo marker of β-AR responsiveness, in 94 healthy participants. The MacArthur Scales of Subjective Social Status were used to assess SSS in the USA (SSS-USA) and in the local community (SSS-C). Objective social status was analyzed by calculating the Hollingshead Two-Factor Index.

Results—β-AR responsiveness was reduced (as indicated by higher CD_{25} values) in participants with lower SSS-USA ($p = .007$) and lower SSS-C ($p < .001$). The relationship between CD_{25} and SSS was particularly robust with respect to SSS-C. Hierarchical regression analyses revealed that SSS-C remained a significant predictor of CD_{25} ($p < .001$) and accounted for 14% of the total variance (32%) in CD_{25} after adjusting for socio-demographic variables (age, ethnicity, gender), health factors (exercise, smoking status, body mass index) and objective social status.

Conclusion—Our results indicate that β-AR function may be an important component of the link between SSS and health.

Keywords

β-adrenergic receptors; cardiovascular risk; Chronotropic 25 Dose; MacArthur Scale of Subjective Social Status; socioeconomic status

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Introduction

Low social status has been associated with several poor health outcomes including cardiovascular disease (CVD), and neuroendocrinological pathways have been proposed to underlie causal pathways (Clark, DesMeules, Luo, Duncan, & Wielgosz, 2009; Wilkinson, 1999). In the last decade, a growing body of research has focused on the link between health and subjective social status (SSS), in addition to objective social factors. SSS refers to the individuals' sense of their place in the social ladder. Prior research shows associations between SSS and several health indicators (e.g. cardiovascular risk, mortality, depression) which persists even after controlling for objective social status or negative affect (Adler, Epel, Castellazzo, & Ickovics, 2000; Ostrove, Adler, Kuppermann, & Washington, 2000; Singh-Manoux, Marmot, & Adler, 2005; Wright & Steptoe, 2005). It was further suggested that SSS might be a more precise measure of the social position since it enables a cognitive averaging of a broader range of status-related information including past and future prospects (Singh-Manoux et al., 2005).

The association between social status and poor cardiovascular outcomes may be partly based on prolonged sympathetic over-activity which involves increased stimulation of the beta adrenergic receptor (β-AR) (Leenen, 1999; Palatini, 2001; Remme, 1998; Triposkiadis et al., 2009). β-ARs mediate several catecholamine-induced end organ sympathetic responses such as vasodilatation, heart rate increase as well as immune functions (Mills & Dimsdale, 1993). Prolonged β-AR over-activity down regulates β-AR responsiveness and has been implicated in the pathophysiology of CVD for example by increasing myocardial energy production, oxidative stress and enhancing apoptotic pathways (Triposkiadis et al., 2009). β-AR responsiveness can be assessed in vitro, through measurement of receptor activity on lymphocytes, or in vivo, by infusing of β-agonists and observing the body sensitivity (Mills & Dimsdale, 1993). Studies using these techniques have shown that factors which may be related to lower SSS predict β-AR function; for example perceived stress in the homeless was related with reduced lymphocyte β-AR density (Dimsdale, Mills, Patterson, Ziegler, & Dillon, 1994), and in vivo β-AR responsiveness was reduced in African-Americans compared to Caucasian-Americans (Jain, Dimsdale, Roesch, & Mills, 2004). Thus, prolonged β-AR over-activation, as indicated by altered β-AR responsiveness, may be one mechanism that mediates the effect of SSS on health.

While prior research has focused on associations between objective social factors and β-AR function (Jain et al., 2004), no studies have examined if SSS predicts the in vivo responsiveness of β-ARs. Considering that i) SSS has been related to cardiovascular health, ii) potential features of low SSS predict β-AR function and iii) β-AR function may be important in the pathophysiology of CVD, we tested the hypothesis that SSS significantly predicts the *chronotropic 25 dose* (CD_{25}), an in vivo marker of β-AR responsiveness and chronic β-AR stimulation respectively (Cleaveland, Rangno, & Shand, 1972).

Method

Participants

Participants were healthy unmedicated volunteers. As part of a larger study on health of African Americans and Caucasian Americans, the study group for isoproterenol testing was roughly evenly divided between Caucasian Americans (20 women and 30 men) and African Americans (20 women and 24 men). Age ranged between 19 and 51 years (see Table 1 for sample characteristics). The study was approved by the University of California, San Diego (UCSD) Institutional Review Board. After prescreening, physical examination by a physician, and giving informed consent, in vivo β-AR function was assessed between 7:00 PM and 9:00 PM.

In Vivo Testing of β-Adrenergic Receptor Responsiveness

The CD_{25} isoproterenol stimulation test was used to assess in vivo β-AR function. CD_{25} refers to the dose of isoproterenol, which is necessary to increase heart rate by 25 beats per minute. Low CD_{25} values indicate high β-AR sensitivity (Cleaveland et al., 1972; Mills & Dimsdale, 1993). Participants were connected to an electrocardiogram monitor to measure heart rate. After a 30-min rest and assessment of basal heart rate, an intravenous low-dose bolus (0.1 μg) of isoproterenol was administered to ensure that no adverse reactions to the drug occurred. Following the 0.1 μg bolus, participants were infused with incremental bolus doses (0.25, 0.5, 1.0, 2.0, 4.0 μg) until an increase of heart rate by 25 beats/min above basal heart rate was observed or until the 4.0 μg bolus was completed. The maximum heart rate after each bolus was calculated as the mean of the three shortest R-R intervals. There was a 5-min time interval between bolus injections. Standardized calculation of CD_{25} values was performed as described previously (Cleaveland et al., 1972).

Social Status and Covariate Measures

Participants completed psychological questionnaires the following day. The MacArthur Scales of Subjective Social Status (see Goodman et al., 2001 for details) were used to assess SSS in the local community (SSS-C) and in the USA (SSS-USA). In short, participants are asked to rate their place on the rung of two "social ladders" in relation to those i) who have the highest and lowest standing in their community (SSS-C) and ii) who are the best and worst off with respect to money, education, and respected jobs in the USA (SSS-USA). Lower scores indicate lower SSS.

Objective social status was considered by calculating the Hollingshead Two-Factor Index (HTFI), a well established indicator of socioeconomic status which is based on weighted values of education and occupation levels (Hollingshead, 1957). Socio-demographic and health-related variables such as age, gender, ethnicity, body mass index (BMI), smoking status (smoker/non-smoker), depression (Center for Epidemiologic Studies-Depression Scale, CES-D, Radloff, 1977) and physical activity (weekly-activity-score of the Godin Leisure Time Exercise Questionaire, Godin & Shephard, 1997) may influence β-AR function (Jain et al., 2004; Mills & Dimsdale, 1993) and may also be confounded with social status and health (Clark et al., 2009). Thus, these variables were considered as control variables.

Statistical Analyses

Statistical analyses were carried out with SPSS version 17.0 for Windows (Chicago, SPSS, Inc.). CD_{25} values above 3 standard deviations were considered to be outliers and treated as missing values. One case was considered as multivariate outlier (CD_{25} and SSS) on the basis of studentized deleted residuals and centered leverage values (Fox, 1991) and excluded. The rate of missing values for CD_{25} was 4 % ($N = 4$). With respect to psychosocial measure and covariates, the rate of missing values was below 6 % ($N = 6$) for each variable. Correlational analyses were used to examine associations between study variables. Hierarchical regression analyses were conducted to examine if SSS explains variance in CD_{25} after taking into account socio-demographic variables, health factors and objective social status (missing values were excluded listwise, resulting in 85 cases for the final multivariate regression analyses).

Results

As shown in figure 1, CD_{25} was significantly related to SSS but not to objective social status (bivariate relationships between study variables are presented in Table 2). Hierarchical regression models were separately conducted for each measure of SSS (entered on step 3) to

adjust for socio-demographic covariates (entered on step 1) and objective socioeconomic status (HTFI was entered on step 2). Results for step 1 indicated that this model significantly explains variance in CD_{25} ($p = 0.019$, $R^2 = 0.173$) with gender ($\beta = -0.341$, $p = 0.002$) being a significant predictor of CD_{25} but not age ($\beta = 0.117$, $p = 0.338$), BMI ($\beta = 0.082$, $p = 0.525$), ethnicity ($\beta = -0.200$, $p = 0.115$), smoking status ($\beta = -0.041$, $p = 0.702$) or exercise ($\beta = -0.136$, $p = 0.212$). Results for step 2 indicated that HTFI was not a significant predictor of CD_{25} ($\beta = 0.080$, $p = 0.490$, $\Delta R^2 = 0.05$). When SSS-C was entered on step 3, SSS-C remained significantly related to CD_{25} ($\beta = -0.393$, $p = 0.000$) and accounted for 14% of the total variance (32%) explained by this model. When SSS-USA was entered on step 3, SSS-USA accounted for 3% of the total variance (22%) explained by this model but failed to reach significance ($\beta = -0.191$, $p = 0.100$).

Because depression may be related to in vitro β-AR function (Mazzola-Pomietto, Azorin, Tramoni, & Jeanningros, 1994) and participants with negative mood may rate themselves low on the SSS ladders (Operario, Adler, & Williams, 2004), exploratory analyses were conducted with socio-demographic covariates on step 1, depression on step 2 and SSS measures on step 3. Results for step 2 indicated that depression was not a significant predictor of CD_{25} after controlling for socio-demographic factors ($\beta = 0.110$, $p = 0.299$, $\Delta R^2 = 0.012$). When SSS-C was entered on step 3, SSS-C remained significantly related to CD_{25} ($\beta = -0.402$, $p = 0.000$) and accounted for 13% of the total variance (32%) explained by this model. When SSS-USA was entered on step 3, SSS-USA failed to be a significant predictor of CD_{25} ($\beta = -0.191$, $p = 0.105$).

A number of exploratory analyses were conducted. Since education and occupation may operate differently, we examined objective social status using separate measures of education and occupation as opposed to the composite HTFI. Moreover, we reran our analyses without participants who were under age 25, because objective social status may be more difficult to ascertain in younger participants. Both approaches did not materially change our basic findings. Finally, because association patterns between social status and health may differ between Caucasian Americans and African Americans (Jain et al., 2004; Ostrove et al., 2000) we examined whether interaction terms (SSS × ethnicity) explained variance in CD_{25} in addition to SSS and ethnicity. Interaction terms did not significantly explain variance in addition to SSS and ethnicity (results of exploratory analyses not shown).

Discussion

Our main finding is that the in vivo responsiveness of β-ARs was reduced (i.e. higher CD_{25} values) in individuals with low SSS. This relationship was robust with respect to SSS in the local community, which remained significantly related to CD_{25} after adjusting for several covariates, including objective social status and depression. β-ARs are important in cardiovascular regulation. Sympathetic over-activity –accompanied by down regulation of β-AR responsiveness– is considered a risk factor for CVD (Leenen, 1999; Mills & Dimsdale, 1993; Palatini, 2001; Remme, 1998; Triposkiadis et al., 2009). Thus, our findings support previous research showing that SSS is related to cardiovascular health (Adler et al., 2000; Cooper et al., 2010; Singh-Manoux et al., 2005). Although the exact pathways by which SSS might influence health are not known, a potential down regulation of β-AR function may result from chronically increased catecholamine levels since hyperactivity of the hypothalamic-pituitary-adrenal axis has been related to lower SSS, and reduced β-AR responsiveness is considered a reliable indicator of chronically increased catecholamine concentrations (Adler et al., 2000; Janicki-Deverts et al., 2007; Mills & Dimsdale, 1993; Wright & Steptoe, 2005).

Consistent with prior research demonstrating that SSS can be a better predictor of health indicators than objective status (Singh-Manoux et al., 2005), we found that SSS but not objective social status influences the whole body sensitivity to β-AR stimulation. Such findings may support the suggestion that SSS is a more precise measure of the social position because it enables a cognitive average of several status-related social variables by taking into account more information of the individual's sociocultural circumstances and also past and future prospects (Singh-Manoux et al., 2005). A further perspective, which is not contradictory to the previous, is that not absolute socioeconomic measures but rather a low relative position, as assessed by the SSS ladders, leads to stress inducing negative emotion resulting in poor health outcomes (Wilkinson, 1999).

We found that the relationship between SSS and CD_{25} was stronger and more robust for SSS-C than for SSS-USA. A similar association pattern has been reported by Ghaed and Gallo (2007) for cardiovascular risk factors (pessimism, stress and increased blood pressure) and may reflect the circumstance that social comparisons with individuals in the local community are everyday occurrences which influence one's psychosocial well-being stronger and more directly than more abstract comparisons with people in the whole country. SSS-C may also enable a more accurately and broader personal assessment of SSS than SSS-USA, since SSS-C also considers factors beside traditional markers of social status (e.g. perceived respect from others, social standing within religious or other social groups) (Ghaed & Gallo, 2007). Our finding that SSS-USA failed to be a significant predictor of CD_{25} in the adjusted models reflects also that SSS-USA was stronger related to covariates (age and BMI) than SSS-C.

Our findings are limited because of the cross-sectional design. Thus, causality in the relation between SSS and β-AR function cannot be determined. Moreover, we cannot exclude that the relationship between SSS and CD_{25} is due to confounding variables, which were not analyzed in this study, although the impact of the most probable covariates (age, gender, ethnicity, BMI, exercise, smoking, objective social status and depression) were carefully examined (see methods). For example, β-AR function decreases with age (Bao et al., 2005; Ebstein, Stessman, Eliakim & Menczel, 1985) and lower social status may be linked to faster aging (Cherkas et al., 2006). Thus, although we control for numerical age, we cannot exclude that the SSS-CD_{25} relationship is partially confounded by physiologic age since physiologic age may not always match numerical age. Moreover, because participants of this study mainly derived from the area of San Diego, CA, the generalizability of our results may be limited.

In conclusion, our findings suggest that lower SSS, particularly within the local community, is related to decreased in vivo β-AR responsiveness (as indicated by higher CD_{25} values). This study extends previous research by suggesting that β-AR function, is one potential mechanism which may mediate, in part, the effect of SSS on health.

Acknowledgments

This work was supported, in part, by Grants by Grants HL36005, HL57269, HL44915 and 1UL1RR031980 from the National Institutes of Health (J.E.D.).

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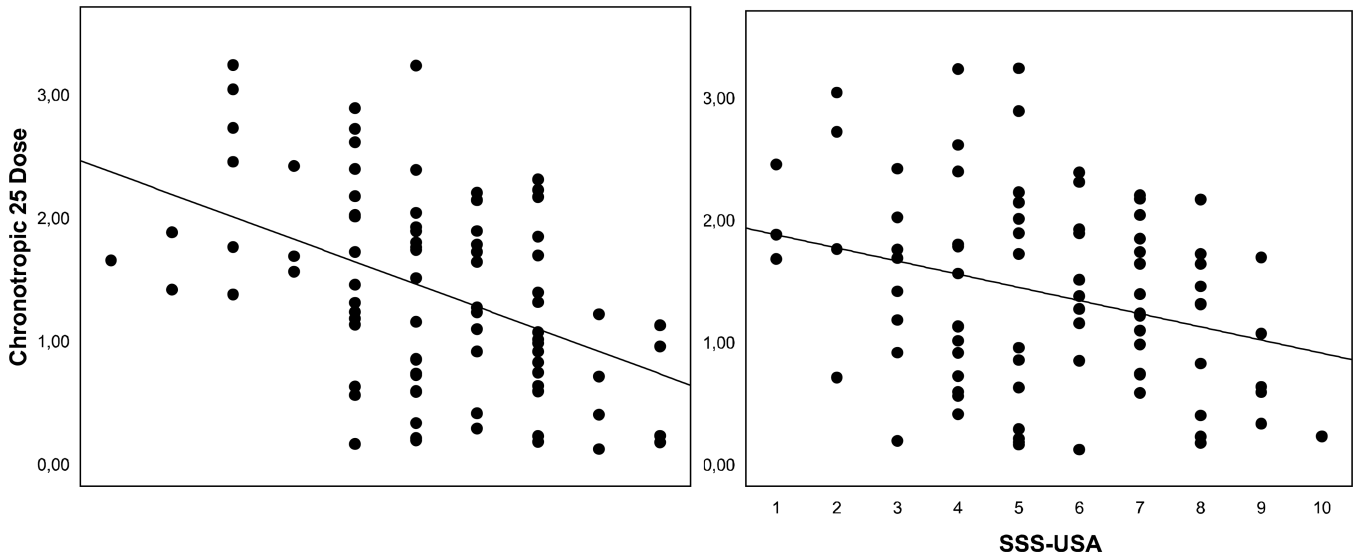

Figure 1.
Individuals with lower subjective social status in the community (SSS-C) and in the USA (SSS-USA) exhibit reduced in vivo β-adrenergic receptor responsiveness (i.e. higher Chronotropic 25 Dose values).

Table 1

Descriptive statistics of study variables (N = 93).

Age, years	35.1 (9.3)
Body mass index, kg/m^2	26.3 (3.7)
Females, N (%)	40 (42.6)
African Americans, N (%)	44 (46.8)
Caucasian Americans, N (%)	50 (53.2)
Hollingshead Two-Factor Index	41.5 (14.5)
Subjective social status in the community	6.3 (2.0)
Subjective social status in the USA	5.5 (2.2)
Center for Epidemiologic Studies Depression Scale	10.7 (9.4)
Current smoker, N (%)	11 (11.7)
Leisure-time exercise	76.8 (123.7)
Baseline heart rate, bpm	65.2 (10.2)
Chronotropic 25 dose, μg	1.4 (0.8)

Note. Values shown as mean (SD) unless otherwise noted.

Table 2

Pearson correlations (r) between study variables.

Variable	CD_{25}	Age	BMI	HTFI	SSS-C	SSS-USA	LTE	HR	CES-D
CD_{25}	–	[.200]	[.202]	.035	−.443***	−.291**	−.035	.092	.105
Age		–	.506***	.044	−.074	[−.184]	.005	.030	−.054
BMI			–	−.153	−.161	[−.202]	−.018	.221*	−.090
HTFI				–	−.057	−.130	.114	.044	.016
SSS-C					–	.567**	.000	−.089	−.367***
SSS-USA						–	−.243*	−.048	−.243*
LTE							–	[−.188]	.016
HR								–	[.192]

Note. BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; CD_{25} = chronotropic 25 dose; HR = baseline heart rate; HTFI = Hollingshead Two-Factor Index; LTE = leisure-time exercise; SSS-C = subjective social status in the community; SSS-USA = subjective social status in the USA.

* $p < 0.05$;

** $p < .01$,

*** $p < .001$,

$p < .1$ in brackets