Title: Social disadvantage and social isolation are associated with a higher resting heart rate: evidence from The Irish Longitudinal Study on Ageing (TILDA).

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ABSTRACT

Objectives: A high resting heart rate (RHR) represents a major risk factor for cardiovascular disease and individuals from poorer backgrounds have a higher RHR compared with their more advantaged peers. This study investigates the pathways through which low socio-economic status (SES) contributes to a higher RHR.

Method: The sample involved data for 4,888 respondents who were participating in the first wave of The Irish Longitudinal Study on Ageing (TILDA). Respondents completed a detailed interview at home and underwent a 5-minute baseline electrocardiograph recording as part of a clinic-based health assessment. SES was indexed using household income.

Results: The mean difference in RHR between those at polarised ends of the income distribution was 2.80 beats per minute (bpm) [CI=1.54, 4.06; $p<0.001$], with the magnitude of the socio-economic differential being greater for men [4.15 bpm; CI=2.18, 6.12; $p<0.001$] compared with women [1.57 bpm; CI=0.04, 3.10; $p<0.05$]. Psychosocial factors including social network size and loneliness accounted for a sizeable proportion of the socio-economic differential in RHR, particularly among men.

Discussion: The finding that poorer people have a higher RHR reinforces the need for additional research exploring the pathways through which social inequalities are translated into biological inequalities.

Keywords: resting heart rate (RHR); socio-economic status (SES); social networks; loneliness; Irish cohort study

INTRODUCTION

A high resting heart rate (RHR) has been identified as a risk factor for cardiovascular disease (CVD) and cardiovascular mortality across a large number of studies (Cooney, Vairtiainen, Laaktainen, Juolevi, Dudina, & Graham, 2010; Jensen, Marott, Allin, Nordestgaard, & Jensen 2012; Kristal-Boneh, Silber Harari, & Froom, 2000), including prospective studies (Jensen et al. 2012; Kristal-Boneh et al. 2000). Indeed, a recent review indicated that heart rate was associated with cardiovascular mortality in 36 of the 38 studies which were included as part of the review (Perret-Guillaume, Joly, & Benetos, 2009).

A separate body of research has shown that there is a pronounced social gradient in relation to CVD and that people from more socially disadvantaged backgrounds are at higher risk of CVD (Fiscella & Tancredi, 2008; Lynch, Kaplan, Cohen, Tuomilehto & Salonen, 1996). For example, data from a large epidemiologic prospective cohort study of men found that those in the bottom 20% of the income distribution were twice as likely to experience cardiovascular mortality and four times more likely to experience acute myocardial infarction at follow-up compared with the wealthiest 20% of the sample (Lynch et al., 1996). Interestingly, a recent study found that those from more disadvantaged soci-economic backgrounds have a higher RHR than their more advantaged peers (Chaix, Jouven, Thomas, Leal, Billaudeau, Bean et al. 2011), which raises the possibility that differences in heart rate may help explain some of the excess risk of CVD among disadvantaged groups; particularly given the finding that a 5 beats per minute increase in RHR is associated with a 17% increase in cardiovascular mortality (Hozawa, Okhubo, Kikuya, Ugajin, Yamaguchi, Asayama, et al. 2004).

The effect of socio-economic status (SES) on CVD is mediated through a number of different processes including early life influences (Dong, Giles, Felitti, Dube, Williams,

Chapman et al. 2004; Smith, McCarron, Okasha, & McEwen, 2001), material deprivation (Fiscella & Tancredi, 2008), psychosocial stresses (Matthews & Gallo, 2011; Steptoe & Kivimaki, 2013), and lifestyle-related factors (Dong et al, 2004; Smith et al, 2001). Investigators have found that anthropometric indicators of impaired foetal growth and development such as low birth-weight, which are socially structured (see Kramer, Sequin, Lydon & Goulet, 2000) represent a major risk factor for CVD in later life (Eriksson, 2011). Material deprivation exerts a direct influence on the quality of nutrition that is accessible to an individual, and people from disadvantaged backgrounds tend to have poorer dietary quality (Ricciuto & Tarasuk, 2007). Similarly, lifestyle factors such as smoking tend to be heavily socially patterned (Hiscock, Bauld, Amos Fidler & Munafò, 2012) and increase risk for adverse cardiovascular outcomes.

Psychosocial factors have also been implicated in the aetiology of CVD because SES predisposes to more stressors while simultaneously constraining the amount of resources one has available to overcome or ameliorate the impact of a stressor (Matthews & Gallo, 2011). The cardiovascular system therefore represents a plausible psychobiological pathway through which social inequalities, mediated via lifestyle factors and psychosocial processes acting over the life-course are translated into biological inequalities that may be prior to the emergence of CVD. Indeed, investigators have tried to quantify the effects of SES induced biological stress using a multi-system, multi-component allostatic load score which usually comprises indices of cardiovascular functioning (Matthews & Gallo, 2011).

In the classical ‘fight or flight’ stress response, sympathetic nervous system activation leads to increased secretion of catecholamines and glucocorticoids, which in turn raise heart rate, respiratory rate and blood pressure. It is assumed this response is transient and that the

physical systems return to baseline. However, recent data suggests that repeated or chronic exposure to stress has lingering end-organ effects, and that excessive levels of catecholamines and their oxidative by-products injure myocardial tissue (Adameova, Abdellatif, & Dhalla, 2009;). A higher RHR might therefore represent the end point of this accumulation of disadvantage over time, reflecting earlier ageing of the vasculature with well-established consequences for CVD risk and life expectancy (Tardif, 2009). It has also been suggested that an elevated RHR may reflect an imbalance in the autonomic nervous system, leading to sympathetic dominance and increased inflammation, which may precipitate atherosclerotic processes (Whelton, Narla, Blaha, Nasir, Blumenthal et al. 2014). Viewed in this way, a higher RHR might well be considered a biomarker of biological ageing.

A recent study provides support for the idea that heart rate is sensitive to social influences (Chaix et al., 2011). These investigators used individual and neighbourhood indicators of disadvantage to create a composite socio-economic index and observed that heart rate increased with increasing socio-economic disadvantage. In univariate analysis, the most disadvantaged group had a resting HR that was 3.6 beats per minute higher on average compared with those in the least disadvantaged group. When adjusted for classical risk factors, sports and exercise participation accounted for the largest proportion of the socio-economic differential (22%); with the other mediating variables – waist circumference (9%), gamma-glutamyltransferase (7%), alkaline phosphatase (5%) and leg length (3%) – accounting for proportionately less. Nevertheless, in multivariable adjustment 53% of the SES-related difference in heart rate remained unexplained, which reinforces the need to examine other risk factors which may contribute to SES-related differences in heart rate. Psychosocial factors represent a potentially fecund area of investigation but have not featured

prominently in the empirical work that has been done to date, at least with respect to socially mediated variation in heart rate (Krantz & McCeney, 2002). Chaix et al. (2011) included measures of perceived stress and depression but these were found to be unrelated to heart rate in the fully adjusted models.

This study builds upon previous work in a number of important ways. Firstly, it employs a broader and more varied definition of the psychosocial environment than has been employed in previous studies by considering the role of inter-personal factors such as social connectedness and loneliness as potential mediators of the social gradient in RHR. People from more disadvantaged social backgrounds have smaller social support networks (Stringhini, Berkman, Ferrie, Marmot, Kivimaki, & Singh-Manoux, 2012; Steptoe, Shankar, Demakakos, & Wardle, 2013). A series of studies have documented links between social isolation and measures of cardiovascular functioning (Hawkley, Thisted, Masi, & Cacioppo, 2010; Steptoe & Kivimaki, 2013). Hawkley et al. (2010) found that loneliness at baseline predicted increases in systolic blood pressure (SBP) at 2, 3 and 4 year follow-up independent of perceived stress, hostility and social support; and that the effect was graded such that higher levels of loneliness predicted higher SBP.

Secondly, the study explores differences separately for males and females as there is reason to suspect that men derive greater health benefits from the availability of social supports compared with women (Stringhini et al., 2012; Unger, McAvay, Bruce, Berkman, & Seeman, 1999). For example, Stringhini et al. (2012) found that structural measures of social support predicted increased risk of mortality among men, but not among women, in a large prospective study of British civil servants over a mean follow-up interval of 20.8 years. Furthermore, social network score and marital status explained 29% of the association

between SES and all-cause mortality in men, which reinforces the necessity of stratifying by gender. Given the working hypothesis that a higher RHR may indicate accumulation of disadvantage over time, we also examine whether SES related differentials become more pronounced as people age. We examine these issues using data from a large population based cohort study of ageing in the Republic of Ireland.

METHODS

STUDY DESIGN AND PARTICIPANTS

The Irish Longitudinal Study on Ageing (TILDA) is a large prospective cohort study examining the social, economic and health circumstances of 8,175 community-dwelling older adults aged 50 years and older resident in the Republic of Ireland. The sample was generated using a 3-stage selection process and the Irish Geodirectory as the sampling frame. The Irish Geodirectory is a comprehensive listing of all addresses in the Republic of Ireland which is compiled by the national post service and ordnance survey Ireland. Subdivisions of district electoral divisions pre-stratified by socio-economic status, age and geographical location served as the primary sampling units. The second stage involved the selection of a random sample of 40 addresses from within each PSU resulting in an initial sample of 25,600 addresses. The third stage involved the recruitment of all members of the household aged 50 years and over. Consequently, the response rate was defined as the proportion of households including an eligible participant from whom an interview was successfully obtained. A response rate of 62.0 percent was achieved at the household level.

There were three components to the survey. Respondents completed a computer assisted personal interview (CAPI) (n=8175) and a separate self-completion paper and pencil module (n=6915) which collected information that was considered sensitive. All participants

were invited to undergo a separate health assessment at one of two national centres using trained nursing staff. 5036 respondents attended the health centre assessment, of which 4891 provided heart rate measurements, which represents the initial case base for the analysis. A more detailed exposition of study design, sample selection and protocol is available elsewhere (Whelan & Savva, 2013).

Ethics Statement

Ethical approval for the study was obtained from the Trinity College Dublin Research Ethics Committee and signed informed consent was obtained from all participants.

OUTCOME VARIABLE – RESTING HEART RATE

Respondents who attended the health centre assessment completed a 5-minute baseline surface electrocardiogram (ECG) recording (Medilog Darwin®). They were instructed to lie supine and breathe normally while measurements were taken. ECG signals were sampled at 4000 Hz, filtered between 0.01–100.0 Hz. Records were scored for significant noise and artefact and cases were excluded (n=3) if noise hampered the clinician's interpretation.

PRIMARY PREDICTOR VARIABLE – SOCIO-ECONOMIC STATUS

Household income, adjusted for the number of respondents living in the household was used to measure socio-economic status. During the course of the household survey, respondents were asked to report all income resulting from full or part-time employment, private or public pensions, and income from other social welfare transfers. Respondents who could not provide an exact figure for income were asked to estimate their income using a banded range: (1) <€10,000 (2) €10,000 - <€20,000 (3) €20,000 - <€40,000; (4) €40,000 -

<€70,000 and (5) >=€70,000. These cases were treated by setting them equal to the mid-point of the banded range. We imputed for the remaining cases missing on income using a multiple imputation procedure (described below). Household income quintiles were then generated among the sample of people who attended the health centre assessment after imputing for income.

COVARIATES

Classical Risk Factors

Two seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were obtained separated by a 1 minute interval using an automatic digital BP monitor (OMRON^{TM}, Model M10-IT). The means of the 2 readings were then averaged to derive SBP and DBP estimates. Medication use was recorded during the household interview and confirmed by cross-checking with the labels on the medicinal packaging. Anatomical Therapeutic Classification (ATC) codes were used for classification (WHO, 2013). Respondents were questioned about angina, heart attack, heart failure, stroke, and transient ischemic attack (TIA). The total number of cardiovascular disease conditions was then summed to create a continuous variable ranging between 0-5. A separate binary variable was used to indicate whether the respondent had ever been diagnosed with diabetes.

Lifestyle Behaviours

Smoking status was indexed using a three level variable: never smoked, past smoker, or current smoker. The CAGE alcohol screening test (Ewing, 1984) was used to index hazardous drinking. The scale comprises 4 items and follows a dichotomous yes/no response format. Answering yes to two or more questions indicates a clinically significant profile and constitutes potentially hazardous drinking. Physical activity was assessed using the 8-item

short form of the International Physical Activity Questionnaire (Craig et al., 2003). It measures the amount of time (mins) spent walking and engaged in moderate and vigorous physical activity, and the amount of time spent sedentary. Scores on this measure were positively skewed because a sizeable proportion of the sample (~10%) were not doing any physical activity. We decided therefore to use a categorical variable representing low, medium and high levels of physical activity as per the IPAQ protocol (www.ipaq.ki.se). We also tried a log-transformation imputing small integer values for individuals' who had a score of zero on the IPAQ, but the results were very similar and the categorical variable has the advantage of being in the original metric.

Lipid Profiles & Anthropometric Measures

Respondents also provided a blood sample during the course of the health assessment and these were sent for immediate analysis to derive a detailed lipid profile which included high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides. Anthropometric measurements were obtained by trained nursing staff using scientifically calibrated and medically approved equipment. Height was measured to the nearest 0.1 centimetre using a SECA 240 wall mounted measuring rod. Weight was measured to the nearest 0.1 kilogram using a SECA electronic floor scales. Waist circumference was measured to the nearest 0.1cm using a SECA measuring tape with the waist defined as the point midway between the iliac crest and the costal margin (lower rib).

Psychosocial Variables

Mental Health

A generalized measure of stress was obtained using the 4-item short form of the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983) which is designed to gauge the

extent to which an individual appraises situations in his/her life as stressful. Sample items include: '*…how often have you felt difficulties were piling up so high that you could not overcome them?*' and respondents indicate how often they have felt this way in the past month on a five point rating scale ranging from 'never' to 'very often'. Scores range from 0 through 16 with higher scores indicating higher levels of perceived stress. The PSS has adequate internal consistency reliability for a short 4-item scale as assessed in the present study using Cronbach's alpha ($\alpha = 0.65$). Cohen and Janicki-Deverts (2012) report that higher scores on the PSS are associated with elevated cortisol levels, suppression of the immune response, and problems with sleep.

Depressive symptoms were indexed using the Centre for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977). It measures the major components of depressive symptomatology, including depressive mood, feelings of guilt and worthlessness, psychomotor retardation, loss of appetite, and sleep disturbance. Respondents are shown 20 statements and asked to rate how often they have felt this week in the past week on a four point (0-3) response scale ranging from *'Rarely or none of the time (less than 1 day)' to 'All of the time (5-7 days).* A total score is calculated by summing responses across the 20 items (range 0-60) with higher scores representing higher levels of depression. The instrument has robust psychometric properties including excellent internal consistency reliability ($\alpha = 0.87$ in the present study), a stable factor structure (Knight, Williams, McGee, & Olaman, 1997), and discriminates well between psychiatric and general population samples (Radloff, 1977).

Social Connectedness

Social connectedness was indexed using the Berkman-Syme Social Network Index (SNI) (Berkman & Syme, 1979) which is a 4 item composite measure comprising different

types of social connections: marital status (married vs not married); sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership (no vs yes) and membership in other community organisations (no vs yes). A total score ranging between 0-4 indicates the extent of social connections with higher scores signifying greater social connection. The SNI demonstrates convergent validity with other measures of social support including the Social Relations Satisfaction Scale (Melchior, Berkman, Niedhammer, Chea & Goldberg, 2003), and scores on this measure are predictive of health and mortality outcomes (Berkman & Syme, 1979). Loneliness was measured using 5 items from the UCLA loneliness scale (version 3) which was designed to assess subjective feelings of loneliness and social isolation (Russell, 1996). Respondents were asked: "how often do you feel you lack companionship?", "how often do you feel left out?", "how often do you feel isolated from others?", "how often do you feel in tune with the people around you?" and "how often do you feel lonely?". Total scores range from 0-10 with higher scores indicating greater feelings of loneliness. Internal consistency reliability for the 5-item scale as assessed in the present study was satisfactory (α= 0.79). The scale has a test-retest reliability of 0.73 over a one-year period and demonstrates convergent validity with other measures of loneliness (Russell, 1996).

Statistical Analysis

All analyses were undertaken in STATA 12.0 using version 1-7-7 of the TILDA dataset. Linear regression analysis was used to examine whether the covariates were predictive of RHR adjusting for age and sex. Wilcoxon rank-sum (non-parametric) and ANOVA one-way (parametric) tests for linear trend were used to test whether the variables that were predictive of RHR in regression analysis were structured according to income. We tested for effect modification by age by fitting income quintile * age interaction terms for the

overall sample, and separately for men and women; however, as none of the interaction terms were significant we pooled the estimates with respect to age. Hierarchical linear regression analysis was used to examine the hypothesis that psychosocial factors partially mediate the association between SES and RHR. The models were initially estimated using complete case analysis (CCA) (n=3760) which reduced the effective sample size by 1128 cases or 23.1%. Sensitivity analyses comparing the characteristics of included and excluded cases revealed that those who were missing listwise on the covariates were more heavily concentrated in lower income groups. This issue was addressed by using a regression based multiple imputation procedure to impute for cases missing on any of the covariates. The multiple imputation by chained equations (MICE) algorithm implemented in STATA 12.0 utilises all non-missing or imputed values to make predictions within a sequential regression-based framework and accommodates variables of different types using an imputation method that is appropriate for each variable.

MI introduces random variation into the imputation process and averages across the simulations to generate a single set of estimates, standard errors and test statistics. The income gradient was found to be steeper, after imputing for missing values, compared with using complete case analysis. This is what we would expect given that individuals' who were missing listwise on any of the covariates tended to be more disadvantaged. Another obvious advantage of his approach is that MI affords greater statistical power. The regression results are therefore presented using the multiply imputed data (n=4888). The data were weighted prior to analysis using survey weights which incorporated both a design weight to account for initial sample design, stratification and clustering, and an additional weighting factor to take account of the fact that respondents who attended the health assessment centre were younger, better educated, and tended to be in better health (Whelan & Savva, 2013).

RESULTS

*** Table 1 here ***

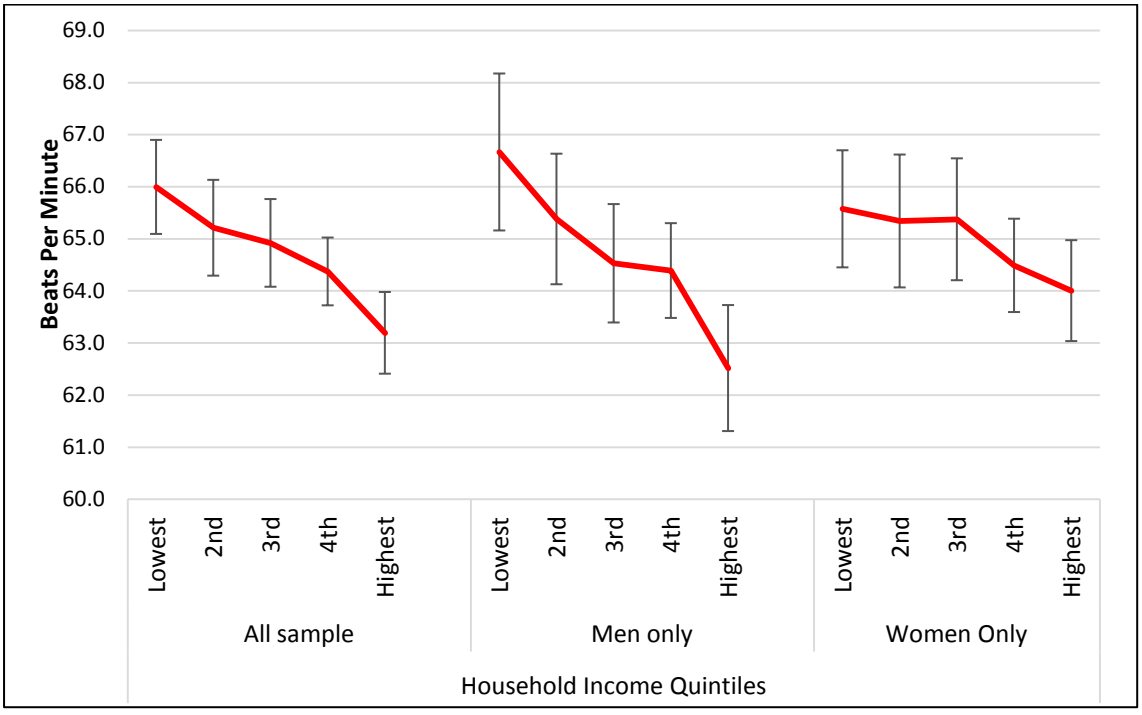
Table 1 describes the baseline characteristics for the overall sample, and separately for males and females. With the exception of low density lipoprotein (LDL), and being a past smoker, all the covariates were predictive of RHR in ordinary least squares regression (OLS). Table 2 shows that the majority of the variables that were predictive of RHR in OLS regression were structured according to income. For example, income was found to be significantly negatively associated with scores on the PSS, CES-D, and UCLA loneliness scale; and significantly positively associated with scores on the SNI, indicating that people from more advantaged socio-economic backgrounds have larger social support networks.

*** Table 2 here ***

Supplementary Figure 1 displays the conditional mean RHR in beats per minute by household income quintiles in the baseline model for the overall sample, and separately for males and females. A clear social gradient was evident in the data with people from lower income backgrounds having a higher RHR. Table 3(a) shows the mean difference in RHR by household income quintiles in the base model (model 1), and the change in the magnitude of the association between RHR and income as the models are adjusted separately for the constellation of classical risk factors (model 2); for the psychosocial factors (model 3); and when adjusted simultaneously for all factors (model 4) in hierarchical linear regression analysis. In the initial model, the difference in RHR between those in the most deprived and

those in the least deprived income groups amounted to 2.80 beats per minute [CI = 1.54, 4.06; p<0.001], with the magnitude of the socio-economic differential decreasing with step increases in income. When entered separately, the set of classical risk factors explained 30% of the difference in RHR between those at the top and the bottom of the income distribution, which was comparable to the amount explained by the psychosocial factors when entered as a block. When the psychosocial variables were entered sequentially (i.e. one at a time – (not shown)) the perceived stress score was associated with a significantly higher RHR, but this relationship no longer held when the social network and loneliness variables were added to the model.

Supplementary Figure 1: Adjusted Average Marginal Resting Heart Rate in Beats Per Minute by Household Income Quintiles (Baseline Model).



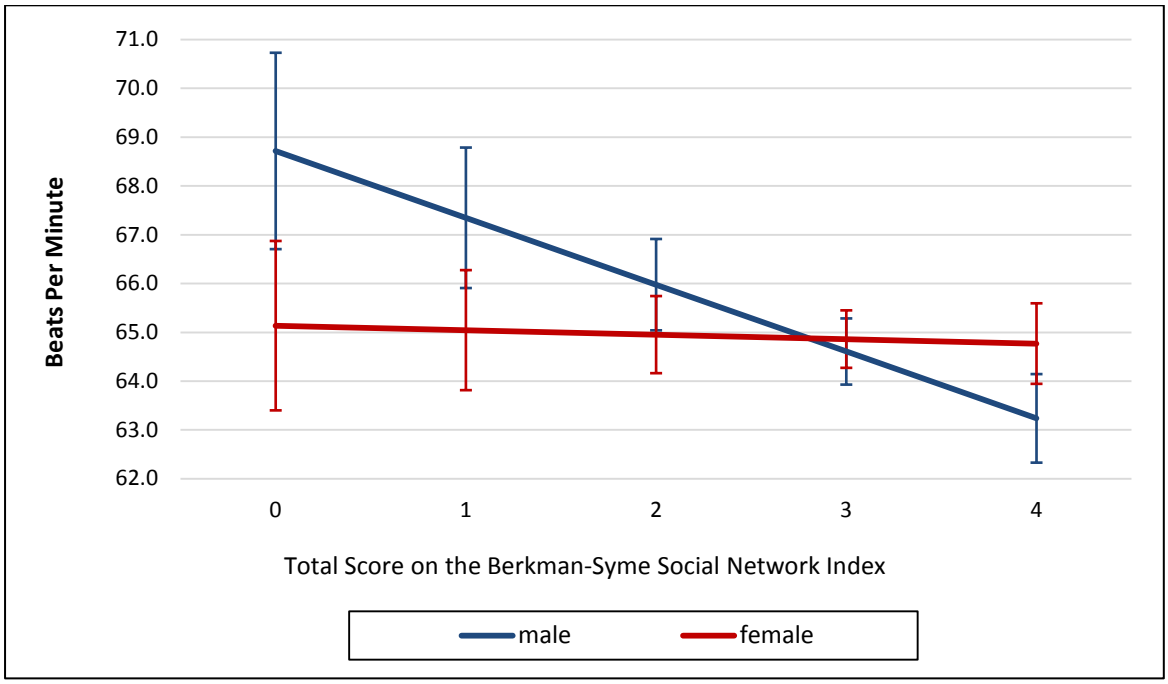
Model adjusted for: age, sex, no. of persons living in household, beta-blockers, calcium channel blockers, SBP, DBP and CVD.

When the classical and psychosocial factors were included in the same model, the difference in RHR between those at the top and bottom of the spectrum was reduced by 50%. In the full multivariable adjusted model, each one unit increase in score on the SNI measure was associated with a reduction of -0.70 bpm [CI=-1.15, -0.25; p<0.01] in RHR. By contrast, each one unit increase in score on the UCLA loneliness measure was associated with a +0.22 bpm increase in RHR [CI=0.01, 0.43; p<0.05].

*** Table 3 here ***

Because the difference in RHR between those at polarised ends of the income spectrum was found to be much steeper for men at 4.15 bpm [CI=2.18, 6.12; p<0.001] compared with women, where the difference amounted to 1.57 bpm [CI=0.04, 3.10; p<0.05], we replicated the analyses separately for males and females as shown in Table 3(b) and 3(c) respectively. With respect to men, psychosocial factors were responsible for a greater diminution of the social gradient in RHR (28.7%) than were the classical risk factors (21%). Again, much of the effect was mediated via the SNI measure. Each one unit increase in score on the SNI measure was associated with a -1.09 [CI=-1.74, -0.44; p<0.001] reduction in RHR in the full multivariable adjusted model. The socio-economic differential in RHR was much less pronounced for women and none of the psychosocial factors were associated with RHR among women. Supplementary Figure 2 shows that there is a significant interaction between sex and SNI score in the full multivariable adjusted model, [$F(1, 616) = 10.99$, p<0.001], indicating that at low levels of social participation, men have a higher RHR compared with women, but at high levels of social participation, men have a lower RHR compared with women.

Supplementary Figure 2: Interaction of Sex with Social Network Score in Prediction of Resting Heart Rate.



Adjusted for age, sex, no. of persons living in household, beta-blockers, calcium channel blockers, SBP, DBP, CVD, diabetes, hazardous drinking, smoking, physical activity, triglycerides, HDL, LDL, waist circumference, height, Social Network Index (SNI), Perceived Stress Scale (PSS), CES-D depression, and UCLA loneliness.

DISCUSSION

In this large epidemiologic based cohort study in the Republic of Ireland, individuals from deprived social backgrounds were found to have a significantly higher RHR compared with their more advantaged peers. In unadjusted analysis, the difference in RHR between those at polarised ends of the income distribution amounted to 2.80 beats per minute, with the magnitude of the socio-economic differential being greater for men (4.15 beats per minute) compared with women (1.57 beats per minute). Why the relationship between income and RHR is so much stronger for men compared with women is not readily apparent, but it is notable that the relationship persists even when the estimates are adjusted for the full battery

of mediating variables, which suggests that the gender difference is not simply attributable to differences in risk factors between males and females. The results of a recent experimental study may provide some insight as it suggests that status ranking may be more important for men compared with women. The study found that men who lost social influence when working with other men had a greater physiological stress response (i.e. cortisol secretion) than they did when they lost influence relative to women. Interestingly, this effect was not evident when women lost influence relative to men, nor indeed when women lost influence relative to other women (Taylor, 2014).

The relationship between life expectancy and total number of heart beats in a lifetime is remarkably similar in mammals (Levine, 1997), which might imply that there is a finite number of beats that can be exercised over a lifetime. The heart is a muscle subject to biomechanical stresses and a higher RHR may precipitate earlier ageing of the organ and more rapid progression to the CVD endpoint. A difference in RHR of 2.80 beats per minute between those at polarised ends of the income distribution scales to an absolute difference of 1,471,580 beats in a year (2,181,240 beats in a year among men): a finding which lends further weight to the idea that differences in heart rate might help explain some of the excess risk in CVD that has been observed among socially deprived groups. Thus RHR may serve as a potent marker of stress induced biological damage in the cardiovascular system.

An obvious difficulty with this interpretation is that women tend to live longer than men despite having a higher RHR. It should be acknowledged, however, that RHR represents the influence of sympathetic and parasympathetic (vagal) nervous systems and the balance of these systems may have different implications for CVD and mortality risk, which may be further modulated by gender specific factors. Palatini (2001) has suggested that the

relationship between tachycardia and adverse cardiovascular events is stronger for men compared with women because they differ in autonomic balance. In men, a higher RHR is hypothesised to reflect higher sympathetic activation whereas in women there is vagal predominance which is cardio-protective. Future work should be directed towards exploring gender differences in autonomic function and whether these are sensitive to social influences.

Given our working hypothesis that low SES is a potent marker of life course stresses and that a higher RHR may encapsulate some of this differential exposure, it might have been expected that the income gradient would become more pronounced as people age. However, this relationship was not evident in the data. In fact, we noticed a tendency for the income effect to dissipate with age in the baseline model when the results were stratified by age group with the association being stronger among those aged less than 65 years compared with those who were older than 65 years (results available upon request). This is not an entirely unexpected finding because a higher RHR is a well established risk factor for cardiovascular mortality, and if disadvantaged individuals are dying earlier, this will necessarily diminish the income gradient as people age.

The analysis went further to ascertain the risk factors that were associated with social inequalities in RHR. While socially mediated variation in exposure to classical risk factors such as smoking and overweight were responsible for a sizeable proportion of the socio-economic differential, the results revealed that psychosocial factors were important too. Specifically, a larger social network size was associated with a lower RHR. Those from more disadvantaged backgrounds were characterised by smaller social networks and higher scores on the UCLA loneliness index. That the social network measure and the loneliness measure were independently associated with RHR in the full multivariable adjusted model

implies that these variables, while related; are not synonymous. This view has been previously articulated by Steptoe et al. (2013) who found that loneliness did not explain the association between social isolation and mortality in their prospective study. Social network size might therefore be more appropriately viewed as a quantitative indicator of the availability of social support, while loneliness reflects a subjective appraisal that the quality and/or quantity of the social network is not sufficient to meet the individual's needs. When the results were disaggregated by gender, psychosocial factors were found to be more important for men than they were for women, a finding which is consistent with other literature examining social group differences in health outcomes among men and women (Ikeda et al. 2007; Stringhini et al. 2012).

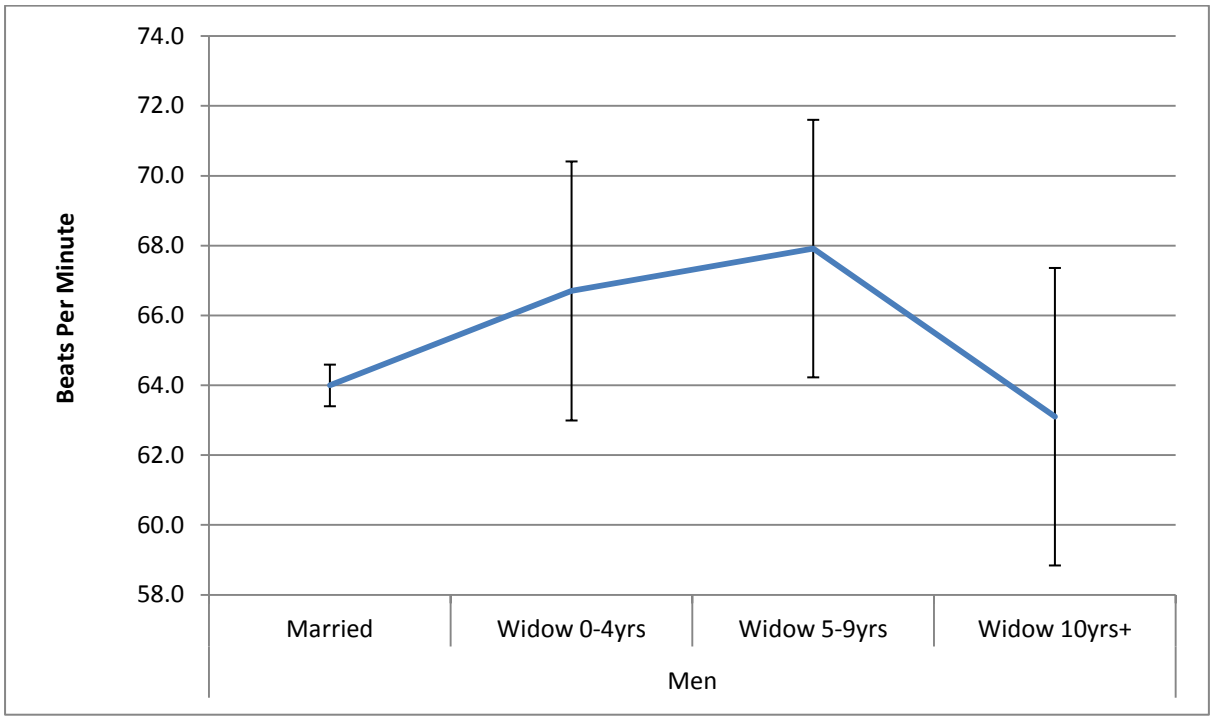
These findings stimulate debate as to how differences in the psychosocial environment translate into a higher RHR. The field of stress physiology arguably provides a mechanism for the biological embedding of social isolation if one interprets social connection as a fundamental human need, and a lack of social support/social integration as a stressor that heightens feelings of vulnerability and promotes vigilance for threat (Hawkley & Cacioppo, 2010). Chronic activation of the stress response can cause dysregulation of hemodynamic, endocrine, and immunologic responses that may compromise cardiovascular functioning (Krantz &Ceney, 2002; McEwen, 2008). Consistent with such a proposition, epidemiologic studies have documented an increase in cardiovascular mortality among socially isolated individuals (Steptoe & Kivimaki, 2013) and widowers (Elwert & Christakis, 2008), and a recent prospective study has documented deleterious effects of childhood isolation for cardiovascular health risk in early adulthood (Caspi, Harrington, Moffitt, Milne, & Poulton, 2006). Alternatively, it could be that the absence of social support means that one does not

benefit from the protection afforded by the presence of social ties in terms of mitigating the impact of a stressor (Cohen & Willis, 1985; Birditt, Newton & Hope, 2014).

Limitations

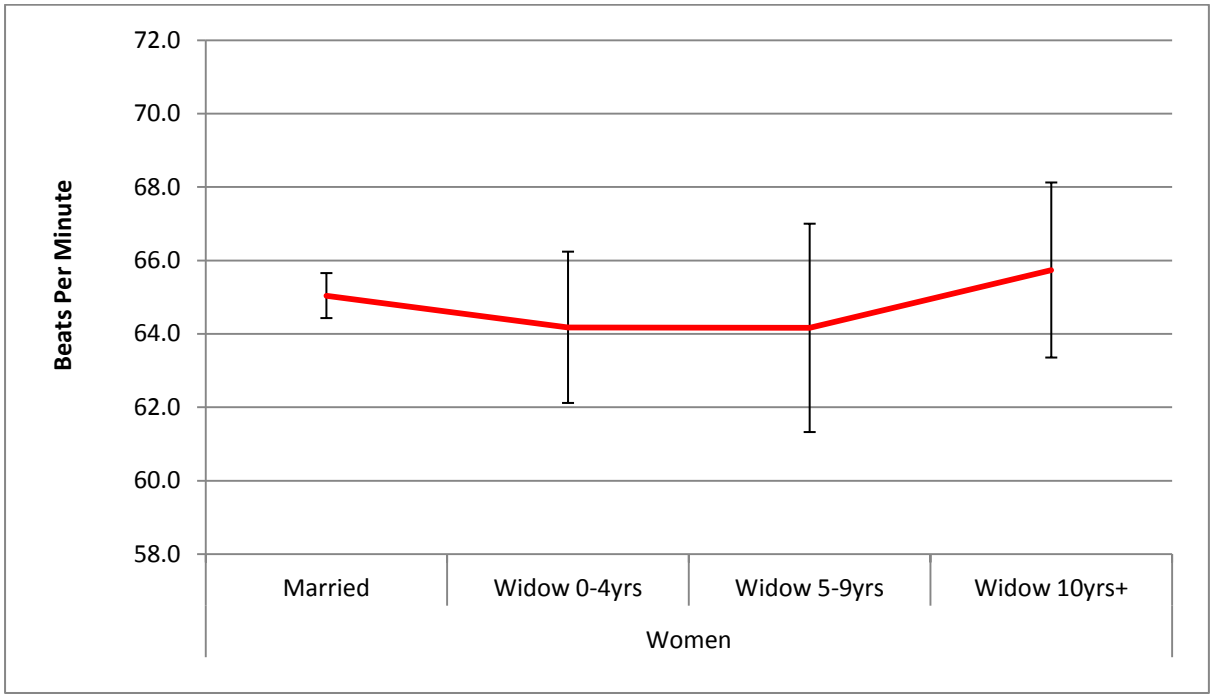
An obvious limitation of the study is that the data were cross-sectional so it could be argued that a higher RHR among those who are more socially isolated reflects reverse causation (i.e. those with existing CVD are less socially engaged because they are in worse health). In an attempt to overcome this difficulty the models were re-estimated, excluding cases with existing cardiovascular disease. Nevertheless, the same broad pattern of results emerged and gender differences were still apparent for both income and the SNI score (results available upon request). As a further test of the hypothesis that psychosocial factors are more important for men compared with women, a supplementary analysis was performed which explored temporal variations in RHR among respondents who had been recently widowed. These results add further weight to the claim that heart rate is responsive to social isolation, particularly amongst men. Supplementary Figure 3a shows that the years following bereavement are characterised by a marked increase in RHR among men relative to those who were married, but no such relationship was evident among women (Supplementary Figure 3b). This result is consistent with evidence from a recent prospective study which found that bereaved men who reported emotional numbness 6 months after the death of their partner had a greater physiological stress response (i.e. cortisol) at 18 months post-loss relative to women (Richardson, Bennett, Carr, Gallagher, Kim et al. 2013).

Supplementary Figure 3a: Adjusted Average Marginal Resting Heart Rate in Beats Per Minute by Bereavement Status (Men only).



Model adjusted for age, beta-blockers, calcium channel blockers, SBP, DBP and existing CVD

Supplementary Figure 3b: Adjusted Average Marginal Resting Heart Rate in Beats Per Minute by Bereavement Status (Women only).



Model adjusted for age, beta-blockers, calcium channel blockers, SBP, DBP and existing CVD

Conclusions

The study also has a number of strengths. Firstly, the study benefits from having a large nationally representative sample which means that the results can be generalised to the population of people aged 50 years and over. Secondly, RHR was measured using electrocardiographic recording over a 5-min resting period. Thirdly, the study examined a greater variety of psychosocial parameters than has been employed in previous research. Finally, the finding that a higher level of social isolation was predictive of a higher RHR and accounts for a substantial proportion of the socio-economic variation in RHR implies that we should be including psychosocial parameters in our psychological and epidemiological discourse regarding socially inequalities in CVD risk.

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***Table 1*: Baseline characteristics of the sample**

Variable	All Sample		Men		Women	
	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N
Resting Heart rate	64.8 (10.7)	4888	64.4 (11.0)	2242	65.2 (10.4)	2646
Systolic Blood Pressure	135.7 (19.5)	4865	138.8 (17.9)	2231	132.7 (20.5)	2634
Diastolic Blood Pressure	82.3 (11.2)	4865	83.4 (10.8)	2231	81.3 (11.5)	2634
Sex	-	4888	48.0%	2242	52.0%	2646
Age	63.3 (9.3)	4880	62.7 (8.8)	2240	63.8 (9.7)	2640
Beta blockers	14.0%	4888	15.6%	2242	12.5%	2646
Calcium channel blockers	9.8%	4888	10.1%	2242	9.5%	2646
No. of CVD's	0.15 (0.46)	4888	0.20 (0.53)	2242	0.11 (0.38)	2646
Diabetes	7.5%	4888	9.4%	2242	5.8%	2646
Median Income (€)	30,000	4495	30,000	2120	25,500	2375
Hazardous drinker	13.4%	4440	18.6%	2026	8.5%	2414
Never smoked	42.3%		35.4%		48.8%	
Past smoker	38.1%	4888	45.1%	2242	31.7%	2646
Current smoker	19.6%		19.5%		19.6%	
IPAQ – low PA	30.3%		25.2%		34.9%	
IPAQ – medium PA	35.0%	4850	32.0%	2222	37.8%	2628
IPAQ – high PA	34.7%		42.9%		27.3%	
Triglycerides	1.76 (1.10)	4772	1.94 (1.19)	2206	1.60 (0.98)	2566
Low density lipoprotein (LDL)	2.90 (0.96)	4772	2.77 (0.95)	2206	3.02 (0.95)	2566
High density lipoprotein (HDL)	1.52 (0.42)	4772	1.34 (0.33)	2206	1.69 (0.43)	2566
Waist circumference (cms)	95.6 (13.8)	4876	101.7 (11.9)	2236	90.0 (13.1)	2640
Height (cms)	165.8 (9.3)	4884	172.9 (6.56)	2241	159.3 (6.21)	2643
Social network index	2.86 (0.88)	4888	2.91 (0.86)	2242	2.81 (0.89)	2646
Perceived stress scale	4.25 (3.14)	4414	4.12 (2.96)	2024	4.37 (3.31)	2390
CES-D	5.97 (7.31)	4825	5.0 (6.34)	2218	6.88 (8.07)	2606
UCLA loneliness	1.98 (2.21)	4422	1.85 (2.09)	2024	2.10 (2.33)	2398

Table 2: Variation in the mediating variables by household income quintiles

Variable	Income 1 (lowest)	Income 2	Income 3	Income 4	Income 5 (highest)	Test for linear trend
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p-value
Male (%)	40.5 [36.1, 45.0]	45.7 [42.2, 49.2]	48.2 [44.9, 51.5]	57.0 [53.8, 60.2]	56.1 [53.6, 58.6]	p<0.001
Age (years)	66.6 [65.5, 67.7]	65.5 [64.6, 66.5]	64.1 [63.3, 64.9]	60.9 [60.1, 61.7]	58.7 [58.1, 59.3]	p<0.001
Systolic Blood Pressure (SBP)	135.9 [133.9, 137.8]	137.4 [135.7, 139.0]	136.2 [134.8, 137.5]	134.6 [133.2, 136.0]	134.1 [132.8, 135.4]	p<0.001
Diastolic Blood Pressure (DSP)	81.6 [80.5, 82.6]	82.0 [81.1, 83.0]	82.1 [81.3, 82.8]	82.6 [81.8, 83.4]	83.2 [82.4, 83.9]	n.s
Beta blockers	17.3 [13.8, 21.5]	17.6 [14.5, 21.1]	15.0 [12.2, 18.3]	11.9 [9.8, 14.4]	9.5 [7.7, 11.7]	p<0.001
Calcium channel blockers	9.1 [6.9, 12.0]	13.3 [10.4, 17.0]	9.7 [7.8, 12.0]	9.6 [7.4, 12.4]	6.2 [4.8, 8.0]	p<0.001
No. of cardio. diseases	0.19 [0.14,0.23]	0.16 [0.12, 0.19]	0.18 [0.14, 0.22]	0.14 [0.10, 0.17]	0.07 [0.05, 0.09]	p<0.001
Diabetes (%)	8.6 [6.3, 11.6]	10.5 [7.9, 13.7]	7.0 [5.2,9.4]	6.9 [5.3, 9.0]	4.6 [3.3, 6.2]	p<0.001
Never smoked (%)	36.2 [31.5, 41.2]	40.4 [36.2, 44.6]	45.1 [41.6, 48.7]	41.0 [37.6, 44.6]	48.5 [45.3, 51.7]	P<0.001
Past smoker (%)	39.2 [34.4 44.2]	37.8 [33.7. 42.1]	35.4 [32.1, 38.9]	40.2 [36.8, 43.6]	38.3 [35.2, 41.5]	n.s
Current smoker (%)	24.6 [20.1, 29.8]	21.8 [18.3, 25.9]	19.5 [16.4, 22.9]	18.8 [15.8, 22.3]	13.2 [11.0, 15.9]	p<0.001
Hazardous drinking (%)	13.7 [10.5, 17.7]	9.3 [7.2, 11.8]	13.3 [10.8, 16.4]	15.4 [12.9, 18.2]	17.1 [14.7, 19.7]	p<0.001
IPAQ – Low PA (%)	36.0 [31.2, 41.0]	31.0 [27.3, 35.0]	28.4 [25.0, 32.0]	28.6 [25.3, 32.2]	25.1 [22.1, 28.4]	p<0.01
IPAQ – Moderate PA (%)	32.9 [28.6, 37.5]	37.4 [33.2, 41.7]	34.2 [30.9, 37.7]	33.8 [30.3, 37.5]	37.2 [34.0, 40.4]	n.s.
IPAQ – High PA (%)	31.1 [26.6, 36.1]	31.6 [27.6, 35.9]	37.4 [33.7, 41.3]	37.6 [33.9, 41.4]	37.8 [34.1, 41.6]	n.s.
Triglycerides	1.77 [1.67, 1.87]	1.77 [1.68, 1.86]	1.73 [1.66, 1.81]	1.81 [1.73, 1.89]	1.72 [1.65, 1.80]	n.s
Low density lipoprotein (LDL)	2.89 [2.80, 2.99]	2.80 [2.71, 2.88]	2.85 [2.79, 2.92]	2.93 [2.86, 3.01]	3.01 [2.95, 3.06]	p<0.01
High density lipoprotein (HDL)	1.55 [1.51, 1.59]	1.47 [1.44, 1.50]	1.53 [1.50, 1.56]	1.50 [1.47, 1.53]	1.54 [1.51, 1.57]	n.s
Height (cms)	163.2 [162.3, 164.1]	164.8 [164.0, 165.5]	165.2 [164.5, 165.8]	168.1 [167.5, 168.7]	168.6 [168.1, 169.2]	p<0.001
Waist circumference (cms)	95.1 [93.7, 96.6]	97.0 [96.0, 98.0]	95.9 [94.9, 96.8]	96.0 [95.1, 97.0]	95.0 [94.1, 95.9]	n.s.
Perceived stress score	4.73 [4.39, 5.07]	4.85 [4.58, 5.11]	4.34 [4.08, 4.60]	3.81 [3.56, 4.05]	3.45 [3.24, 3.66]	p<0.001
Social Network index	2.46 [2.38, 2.54]	2.79 [2.72, 2.87]	2.93 [2.86, 3.01]	2.95 [2.89, 3.02]	3.13 [3.07, 3.19]	p<0.001
CES-D	7.71 [6.80, 8.62]	6.15 [5.48, 6.82]	5.88 [5.22, 6.54]	4.98 [4.46, 5.50]	4.55 [4.10, 4.99]	p<0.001
UCLA loneliness	2.68 [2.42, 2.94]	2.19 [2.00, 2.38]	1.92 [1.72, 2.12]	1.75 [1.58, 1.93]	1.29 [1.17, 1.41]	p<0.001

Table 3: Attenuation of the social gradient in Resting Heart Rate (RHR) in Hierarchical Linear Regression Analysis.

	(a) All Sample (n=4888)							
	Model 1 (Initial)		**Model 1 + classical risk factors**		**Model 1 + psychosocial risk factors**		**Model 1 + classical and psychosocial risk factors**	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Income 1 (lowest)	2.80***	[1.54, 4.06]	1.96**	[0.70, 3.23]	1.96**	[0.66, 3.26]	1.41*	[0.12, 2.70]
Income 2	2.02***	[0.81, 3.23]	1.21*	[0.01, 2.41]	1.49*	[0.27, 2.72]	0.86	[-0.35, 2.07]
Income 3	1.73**	[0.59, 2.86]	1.24*	[0.13, 2.36]	1.41*	[0.28, 2.53]	1.04	[-0.07, 2.15]
Income 4	1.18*	[0.18, 2.18]	0.99	[-0.01, 2.00]	1.04*	[0.03, 2.05]	0.89	[-0.12, 1.91]
Income 5 (highest)	REF	-	REF	-	REF	-	REF	-
Social Network Index	-	-	-	-	-0.87***	[-1.34, -0.41]	-0.70**	[-1.15, -0.25]
Perceived Stress Scale	-	-	-	-	0.11	[-0.05, 0.27]	0.06	[-0.09, 0.21]
CES-D depression	-	-	-	-	0.01	[-0.06, 0.08]	-0.02	[-0.08, 0.05]
UCLA loneliness	-	-	-	-	0.19	[-0.03, 0.41]	0.22*	[0.01, 0.43]
	(b) Men (n=2242)							
Income 1 (lowest)	4.15***	[2.18, 6.12]	3.28***	[1.36, 5.19]	2.96**	[0.94, 4.98]	2.42**	[0.48, 4.37]
Income 2	2.86**	[1.09, 4.63]	2.11*	[0.36, 3.86]	2.23*	[0.45, 4.00]	1.66	[-0.09, 3.41]
Income 3	2.01*	[0.32, 3.70]	1.55	[-0.08, 3.18]	1.63	[-0.07, 3.32]	1.30	[-0.32, 2.91]
Income 4	1.87*	[0.34, 3.41]	1.73*	[0.23, 3.24]	1.72*	[0.19, 3.25]	1.61*	[0.12, 3.11]
Income 5 (highest)	REF	-	REF	-	REF	-	REF	-

Social Network Index	-	-	-	-	-1.36***	[-2.03, -0.69]	-1.09***	[-1.74, -0.44]
Perceived Stress Scale	-	-	-	-	0.19	[-0.03, 0.40]	0.12	[-0.09, 0.32]
CES-D depression	-	-	-	-	0.00	[-0.10, 0.11]	-0.05	[-0.16, 0.05]
UCLA loneliness	-	-	-	-	0.12	[-0.19, 0.44]	0.22	[-0.09, 0.53]
	(c) Women (n=2646)							
Income 1 (lowest)	1.57*	[0.04, 3.10]	0.73	[-0.80, 2.27]	1.06	[-0.51, 2.62]	0.43	[-1.12, 1.98]
Income 2	1.34	[-0.29, 2.96]	0.43	[-1.11, 1.97]	0.96	[-0.68, 2.60]	0.21	[-1.35, 1.76]
Income 3	1.37	[-0.06, 2.80]	0.74	[-0.66, 2.15]	1.14	[-0.27, 2.56]	0.62	[-0.78, 2.02]
Income 4	0.48	[-0.81, 1.78]	0.30	[-0.96, 1.55]	0.38	[-0.91, 1.67]	0.23	[-1.02, 1.49]
Income 5 (highest)	REF	-	REF	-	REF	-	REF	-
Social Network Index	-	-	-	-	-0.40	[-1.01, 0.22]	-0.30	[-0.89, 0.29]
Perceived Stress Scale	-	-	-	-	0.05	[-0.17, 0.27]	0.01	[-0.20, 0.22]
CES-D depression	-	-	-	-	0.01	[-0.07, 0.10]	0.01	[-0.07, 0.09]
UCLA loneliness	-	-	-	-	0.21	[-0.12, 0.54]	0.19	[-0.12, 0.50]

***significant at the 0.001 level, **significant at the 0.01 level, * significant at the 0.05 level

Model 1: adjusted for age, (sex- all sample) no. of persons living in household, beta-blockers, calcium channel blockers, SBP, DBP and CVD.

Model 2: Model 1 + diabetes, hazardous drinking, smoking, physical activity, triglycerides, HDL, LDL, waist circumference, height.

Model 3: Model 1 + Social Network Index (SNI), Perceived Stress Scale (PSS), CES-D depression, and UCLA loneliness.

Model 4: Model 1 + diabetes, hazardous drinking, smoking, physical activity, triglycerides, HDL, LDL, waist circumference, height, SNI, PSS, CES-D, and UCLA loneliness.