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RESEARCH LETTER

Influence of stressful life events and personality traits on *PLN* cardiomyopathy severity: an exploratory study

E. van Drie [1,2*†], S.E.L. Taal [1], A.F. Schmidt[3,4,5], T.E. Verstraelen [6†], R. de Brouwer [7†], D. Schoormans [8], P.M.C. Mommersteeg [8], R.A. de Boer [9], A.A.M. Wilde [6†], F.W. Asselbergs [6,10†], A.F. Baas[1†], J.P. van Tintelen [1†], and L.M. van den Heuvel [1,2†]

[1]Department of Genetics, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; [2]Netherlands Heart Institute, Moreelsepark 1, 3511 EP Utrecht, The Netherlands; [3]Department of Cardiology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; [4]Institute of Cardiovascular Science, Faculty of Population Health, University College London, London, UK; [5]UCL British Heart Foundation Research Accelerator Centre, London, UK; [6]Heart Centre, Department of Cardiology, Amsterdam UMC Location University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands; [7]Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands; [8]Department of Clinical and Medical Psychology and Center of Research on Psychological Disorders and Somatic Diseases (CoRPS), Tilburg University, PO Box 90153, 5000 LE Tilburg, The Netherlands; [9]Department of Cardiology, Erasmus Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; and [10]Health Data Research UK and Institute of Health Informatics, University College London, London, UK

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Clinical features related to the *phospholamban* (*PLN*) gene c.40_42delAGA; p.(Arg14del) pathogenic variant, which may lead to dilated (DCM) or biventricular arrhythmogenic cardiomyopathy (ACM), are highly variable.[1] Phenotypes range from subtle electrocardiogram abnormalities at senescence to sudden cardiac death (SCD) or end-stage heart failure (HF) at a young age.[1] This variability—even between relatives—remains largely unexplained and may be influenced by both genetic and non-genetic factors. One of these non-genetic factors could be psychological distress, which has been linked to increased susceptibility for developing severe phenotypes in inherited cardiomyopathies and channelopathies.[2–5] The association of acute stress with life-threatening arrhythmias and cardiac dysfunction in catecholaminergic polymorphic ventricular tachycardia and ACM, respectively, has been previously documented.[2,3] Although this association is unclear for chronic stress and personality traits, these have previously been associated with coronary heart disease.[6,7] Our study therefore aimed to evaluate the association between chronic stress, personality traits, and major disease manifestations in carriers of *PLN* p.(Arg14del).

Between March 2019 and 2021, we invited both probands and relatives with *PLN* p.(Arg14del) (>18 years). They were asked to once fill out four validated questionnaires about chronic stress, measuring the sum of (i) accumulated stressful life events experienced in different age categories [Long-term Difficulties Inventory (LDI)][8] and (ii) distressed (Type D) personality [Type D scale-14 (DS-14)][9,10] and other personality traits [(c-1) extraversion and neuroticism (Eysenck Personality Questionnaire Revised Short Scale)[11] and (c-2) optimism (Life Orientation Test-Revised)].[12] The primary outcome measure was a major disease manifestation, defined as a composite of the first occurrence of malignant ventricular arrhythmias [MVA; (sustained) ventricular tachycardia/fibrillation, appropriate implantable cardioverter defibrillator (ICD) therapy, and (aborted) SCD] or HF-related events (hospitalization, ventricular assist device, cardiac transplantation, and death). Secondary outcome measures were the separate components of the primary outcome. Clinical characteristics were retrospectively retrieved from health record data collected from the first cardiac evaluation and follow-up visits as part of regular care, as described before.[13] Cox proportional hazard regression analyses were performed adjusting for the covariates sex and educational level and right censored at last cardiac evaluation or death if no event occurred. Time was modelled from birth to increase power, as personality traits were

* Corresponding author. Tel: +31887553800. *E-mail address*: e.vandrie@umcutrecht.nl
† Member of the European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart: ERN GUARD-Heart (ERN GUARDHEART; http://guardheart.ern-net.eu).

Table 1 Association of chronic stress, personality traits, and major disease manifestations in *PLN* p.(Arg14del) carriers and separate outcomes from birth on with and without adjusting for demographic characteristics using cox proportional hazard analyses

	Major disease manifestations (composite endpoint)				Malignant ventricular arrhythmia (MVA, subgroup)				Heart failure-related event (HF, subgroup)			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Type D personality[b]												
Negative affect (NAc)	1.033 (0.994–1.074)	0.103	1.036 (0.995–1.080)	0.089	1.013 (0.967–1.062)	0.584	1.020 (0.971–1.072)	0.435	1.046 (0.993–1.102)	0.089	1.034 (0.980–1.091)	0.218
Social inhibition (SIc)	1.039 (0.996–1.083)	0.074	1.039 (0.996–1.084)	0.079	1.043 (0.994–1.095)	0.087	1.038 (0.988–1.090)	0.138	1.007 (0.950–1.066)	0.823	1.044 (0.979–1.113)	0.611
Interaction NAc*SIc	0.998 (0.990–1.006)	0.605	0.999 (0.990–1.007)	0.763	1.000 (0.991–1.010)	0.943	1.002 (0.992–1.011)	0.718	0.994 (0.983–1.005)	0.289	0.992 (0.981–1.004)	0.191
Personality traits												
Neuroticism	1.023 (0.939–1.114)	0.603	1.024 (0.937–1.120)	0.596	1.004 (0.907–1.111)	0.937	1.014 (0.913–1.126)	0.793	1.027 (0.915–1.153)	0.647	1.002 (0.889–1.129)	0.977
Extraversion	0.987 (0.903–1.079)	0.772	0.989 (0.905–1.082)	0.813	0.957 (0.864–1.059)	0.396	0.966 (0.872–1.069)	0.502	1.071 (0.944–1.215)	0.287	1.060 (0.932–1.206)	0.376
Optimism	0.968 (0.913–1.027)	0.285	0.958 (0.901–1.019)	0.177	0.951 (0.890–1.018)	0.152	0.940 (0.876–1.009)	0.087	0.958 (0.883–1.038)	0.293	0.966 (0.890–1.048)	0.404

All variables were analysed separately. Values are given as hazard ratios, 95% confidence intervals, and *P*-values.

[a]Adjusted for sex and educational level.

[b]Type D personality compromised two subscales on negative affectivity (tendency to experience negative emotions and social inhibition and tendency to inhibit emotion and behaviour in social situations). We used the mean-centred sum scores of both the negative affect (NAc) and social inhibition (SIc) subscales separately and the interaction as variable in the regression analyses.

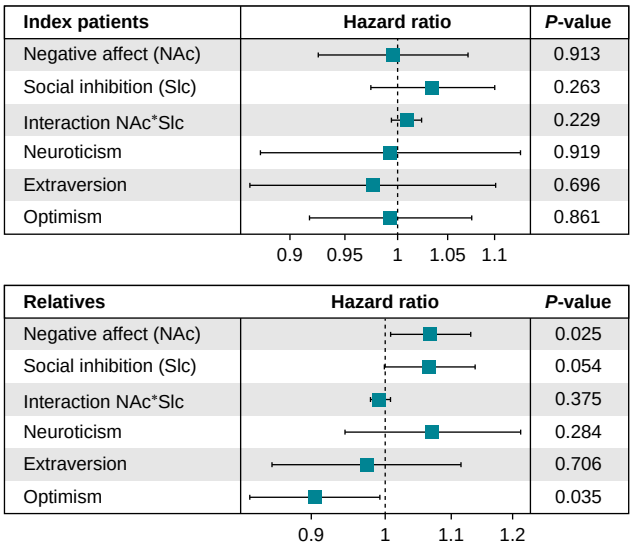

Figure 1 Forest plots of hazard ratios between chronic stress, personality traits, and major disease manifestations restricting to probands or relatives with *PLN* p.(Arg14del). All variables were analysed separately. Values are showed as hazard ratios, 95% confidence intervals and *P*-values. All analyses were adjusted for sex and educational level. Type D personality compromised two subscales on negative affectivity (tendency to experience negative emotions and social inhibition and tendency to inhibit emotion and behaviour in social situations). We used the mean-centred sum scores of both the negative affect (NAc) and social inhibition (Slc) subscales separately and the interaction as variable in the regression analyses.

considered relatively stable over time.[14] However, stressful life events throughout life may change over time. Therefore, we used logistic regression using a lifetime LDI score (sum score for all applicable age categories in the questionnaire),[8] also adjusting for the aforementioned covariates and age of first presentation for suspected inherited cardiac disease or family screening. Regression analyses were repeated within subgroups restricting to probands or relatives. The study protocol was approved by the Medical Ethics Committee (#W19_062).

In total, 377 of 832 (45%) carriers consented for study participation and completed at least one questionnaire. Of these, 22 were excluded due to incomplete or absent data, leaving 355 participants for analysis. Median age was 54 years [interquartile range (IQR) 43–65 years], 43% were male, 19% were probands, and 46% had a high educational level. The median left ventricular ejection fraction among affected participants was 50% (IQR 43–55%), and in 40%, an ICD was implanted. Of all participants, 22% were diagnosed with DCM and 37% with ACM.

A major disease manifestation was present in 78 (22%) participants. Between participants with and without major disease manifestations, we found no difference in median scores of stressful life events throughout life and personality traits. Multivariable logistic regression adjusted for sex and educational level showed no significant association between lifetime LDI scores and major disease manifestations [odds ratio (OR) (95% CI) = 1.024 (0.993–1.054); $P = 0.124$], nor when restricting to probands [OR (95% CI) = 1.019 (0.962–1.085); $P = 0.536$] or relatives [OR (95% CI) = 0.992 (0.942–1.039); $P = 0.756$], or, for the separate outcomes, HF [OR (95% CI) = 1.029 (0.991–1.067); $P = 0.120$] and MVA [OR (95% CI) = 1.023 (0.989–1.056); $P = 0.175$]. Cox regression analyses revealed that Type D personality and the presence of other personality traits were not significantly associated with major disease manifestations or separate components of this outcome (*Table 1*). In separate subgroup analyses restricting to probands or relatives, significant associations were found between a DS-14 subscale and optimism and the age at which a primary outcome occurred in relatives (*Figure 1*). However, after correcting for multiple testing, this association did not sustain.

To conclude, we found no significant associations between chronic stress, personality traits, and major disease manifestations in *PLN* p.(Arg14del). This study is the first to explore the association between chronic stress and major disease manifestations in inherited cardiomyopathies. Previous studies did find an association between primary arrhythmia syndromes or ACM and acute stress rather than chronic stress.[2,3] Only one study explored the role of chronic stress in long QT syndrome and found that stressful life events were associated with life-threatening arrhythmias.[15]

Methodological heterogeneity between our study and previously conducted studies likely contributed to differences in study findings (i.e. differences in participants, acute vs. chronic stressors and outcome measures). In addition, differences in study findings may be caused by pathophysiological differences across diseases. Recent literature suggests that disturbance of the sympathetic adrenal medullary (SAM) axis and the hypothalamic–pituitary–adrenal (HPA) axis (both involved in the stress response) might influence cardiomyocyte function.[16,17] However, in heterozygous *PLN* p.(Arg14del) mice, stimulation of the SAM axis did not lead to earlier disease onset.[18] Personality and chronic stress may also affect disease progression in inherited cardiomyopathies through so-called allostatic load. This implies that stressors and life events accumulate, resulting in chronic activation of the HPA axis, leading to wear and tear on the body.[19] Furthermore, participants were potentially subjected to bias due to its retrospective design (e.g. selection bias, including survivorship and participation bias, or recall bias). As an example of recall bias, patients might experience a stressful episode as more or less stressful than in the past. Another limitation of the present study is the unavailability of reliable, thorough, and comprehensive historical beta-blocker usage data, owing to the challenge of collecting such data accurately. Also, no data on psychological support were available.

Although this exploratory study did not identify significant associations between chronic stress, personality traits, and major disease manifestations, we believe that further research is warranted to thoroughly assess the role of psychological stressors and personality traits in *PLN*

p.(Arg14del) cardiomyopathy and inherited cardiomyopathies in general.

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Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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