

Supplementary Online Content

Huang M, Shah A, Su S, et al. Association of depressive symptoms and heart rate variability in Vietnam War–era twins: a longitudinal twin difference study. *JAMA Psychiatry*. Published online May 16, 2018. doi:10.1001/jamapsychiatry.2018.0747

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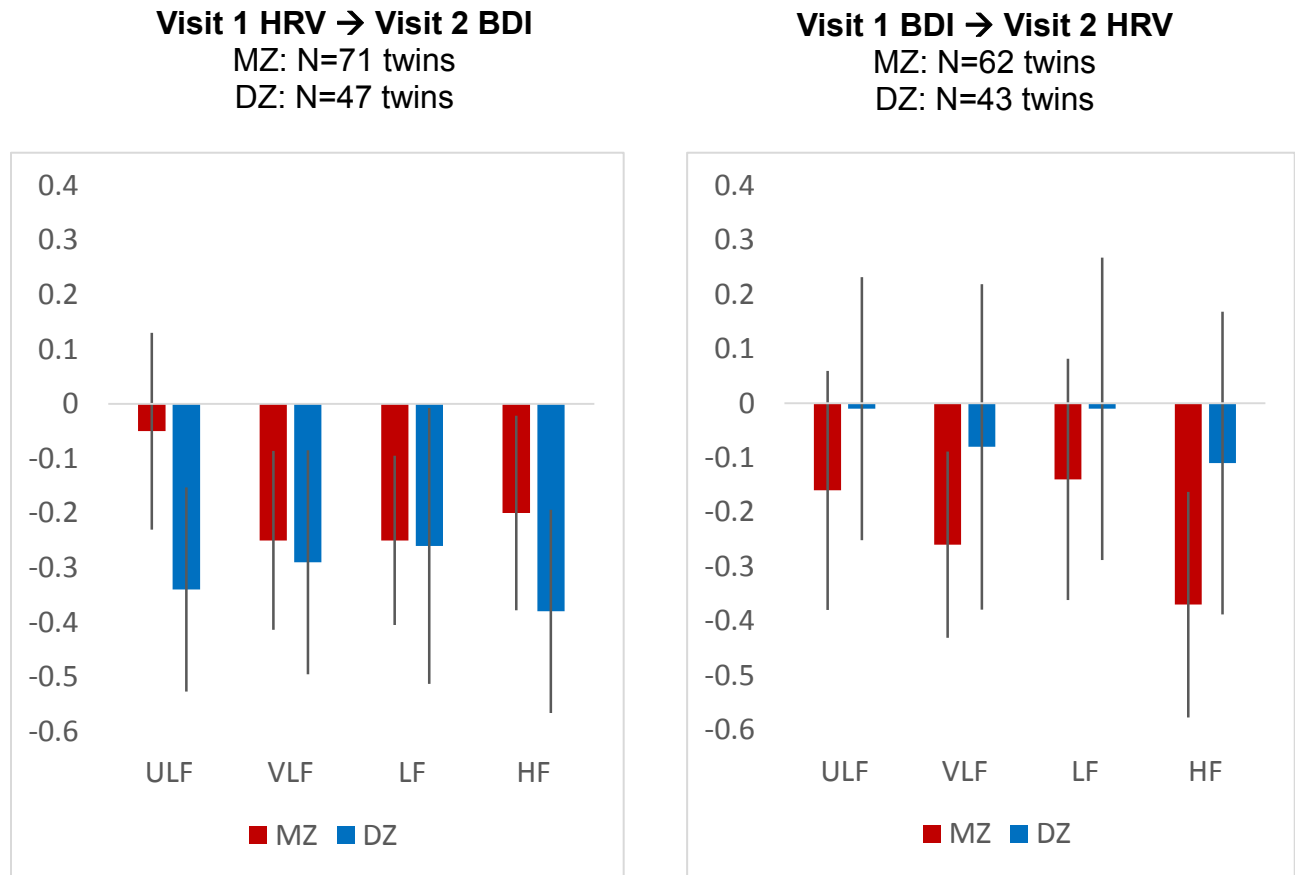
This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Supplemental methods

Measurement of heart rate variability

To evaluation of HRV, subjects wore a Holter monitor (Marquette SEER Light digital system) for 24 hours. Both twins in the same pair were evaluated at the same time, and their recording times, schedule, and activity level during each recording were similar. To further ensure accuracy and comparability of HRV measurements, twins were refrained from smoking, drinking alcohol, and having coffee during measurements, and activities were restricted to quiet walking. Each tape was manually processed and edited to ensure accurate identification of QRS complexes. We used frequency-domain methods to analyze the HRV data, utilizing customized software to assign bands of frequency and then count the number of beat-to-beat intervals that match each band. Each tape of Holter recordings was digitally sampled, processed, and analyzed using a GE Medical/Marquette system, with methods described in the literature.^{30,42} The file was first edited to remove ectopics and noise, and gaps filled in by interpolated linear splines. A heart rate power spectrum analysis was conducted using a fast Fourier transform with a Parzen window on the 24-hour RR interval file, and was corrected for attenuation due to windowing and sampling. Twins whose recordings showed >20% interpolation or <18 recorded hours were excluded from the analysis. The power spectrum was integrated over four discrete frequency bands: ultra-low frequency (ULF), <0.0033 Hz; very low frequency (VLF), 0.0033-<0.04 Hz; low frequency (LF), 0.04-<0.15 Hz; and high frequency (HF), 0.15-<0.40 Hz.^{11,43} HRV data were collected at both visits using identical methodology, and data processing was performed blindly to twins' depression status or other characteristics.

eFigure. Standardized parameter estimates for the longitudinal association in Model 1 (base model), stratified by zygosity



Abbreviations: HRV: heart rate variability; BDI: Beck depression inventory; MZ: monozygotic; DZ: dizygotic; ULF: ultra-low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency.

* Vertical lines indicate 95% confidence intervals.

eTable 1. Baseline cross-sectional association between HRV and BDI

	ULF		VLF		LF		HF	
	ULF → BDI	BDI → ULF	VLF → BDI	BDI → VLF	LF → BDI	BDI → LF	HF → BDI	BDI → HF
Model 1	-0.16	-0.19*	-0.29*	-0.32*	-0.35*	-0.43*	-0.32*	-0.34*
Model 2	-0.10	-0.09	-0.24*	-0.24*	-0.33*	-0.32*	-0.30*	-0.28*
Model 3	-0.10	-0.08	-0.25*	-0.24*	-0.34*	-0.33*	-0.30*	-0.27*
Model 4	-0.07	-0.10	-0.16	-0.20	-0.17	-0.22*	-0.15	-0.17

Abbreviations: HRV: heart rate variability; BDI: Beck depression inventory; ULF: ultra-low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency; CVD: cardiovascular disease; CAD: coronary heart disease; BMI: body mass index.

Results are shown as standardized beta-coefficients in linear regression models. **Model 1:** base model; **Model 2:** model 1 + confounding factors, including smoking, beta-blocker, education, alcohol, physical activity, prevalent CAD; **Model 3:** model 2 + CVD risk factors, including BMI, hypertension, diabetes; **Model 4:** model 3 + antidepressant use.

*indicates significant association at $p < 0.05$.

eTable 2. 7-year follow-up cross-sectional association between HRV and BDI

	ULF		VLF		LF		HF	
	ULF → BDI	BDI → ULF	VLF → BDI	BDI → VLF	LF → BDI	BDI → LF	HF → BDI	BDI → HF
Model 1	-0.18*	-0.19*	-0.39*	-0.34*	-0.40*	-0.40*	-0.38*	-0.38*
Model 2	-0.11	-0.11	-0.27*	-0.20*	-0.20*	-0.17*	-0.22*	-0.23*
Model 3	-0.10	-0.13	-0.22*	-0.15	-0.13	-0.13	-0.19*	-0.24*
Model 4	-0.15*	-0.18	-0.17	-0.11	-0.04	-0.04	-0.14	-0.15

Abbreviations: HRV: heart rate variability; BDI: Beck depression inventory; ULF: ultra-low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency; CVD: cardiovascular disease; CAD: coronary heart disease; BMI: body mass index.

Results are shown as standardized beta-coefficients in linear regression models. **Model 1:** base model; **Model 2:** model 1 + confounding factors, including smoking, beta-blocker, education, alcohol, physical activity, prevalent CAD; **Model 3:** model 2 + CVD risk factors, including BMI, hypertension, diabetes; **Model 4:** model 3 + antidepressant use.

*indicates significant association at $p < 0.05$.

eTable 3. Longitudinal association between HRV and BDI somatic subscale

	visit 1 HRV → visit 2 BDI			
	ULF	VLF	LF	HF
Model 1 (Base model)	-0.20*	-0.26*	-0.25*	-0.33*
Model 2 (Model 1 + confounding factors)	-0.14*	-0.18*	-0.19*	-0.25*
Model 3 (Model 2 + CVD risk factors)	-0.13	-0.19*	-0.21*	-0.27*
Model 4 (Model 3 + antidepressant use)	-0.12	-0.18*	-0.20*	-0.27*
	visit 1 BDI → visit 2 HRV			
	ULF	VLF	LF	HF
Model 1 (Base model)	-0.20*	-0.20*	-0.14	-0.32*
Model 2 (Model 1 + confounding factors)	-0.21*	-0.20*	-0.11	-0.28*
Model 3 (Model 2 + CVD risk factors)	-0.21*	-0.19*	-0.07	-0.28*
Model 4 (Model 3 + antidepressant use)	-0.20*	-0.08	0.04	-0.22*

Abbreviations: HRV: heart rate variability; BDI: Beck depression inventory; ULF: ultra-low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency; CVD: cardiovascular disease; CAD: coronary heart disease; BMI: body mass index.

Results are shown as standardized beta-coefficients in linear regression models.

Model 1: base model adjusted for within-pair difference of baseline dependent and independent variable, and between-pair difference of baseline independent variable; **Model 2:** model 1 + confounding factors, including smoking, beta-blocker, education, alcohol, physical activity, prevalent CAD; **Model 3:** model 2 + CVD risk factors, including BMI, hypertension, diabetes; **Model 4:** model 3 + antidepressant use.

* indicates significant association at $p < 0.05$.

eTable 4. Longitudinal association between HRV and BDI cognitive subscale

	visit 1 HRV → visit 2 BDI			
	ULF	VLF	LF	HF
Model 1 (Base model)	-0.15*	-0.24*	-0.23*	-0.21*
Model 2 (Model 1 + confounding factors)	-0.13*	-0.21*	-0.21*	-0.12
Model 3 (Model 2 + CVD risk factors)	-0.12	-0.22*	-0.23*	-0.15*
Model 4 (Model 3 + antidepressant use)	-0.12	-0.21*	-0.20*	-0.12
	visit 1 BDI → visit 2 HRV			
	ULF	VLF	LF	HF
Model 1 (Base model)	-0.10	-0.26*	-0.10	-0.20*
Model 2 (Model 1 + confounding factors)	-0.12	-0.25*	-0.13	-0.22*
Model 3 (Model 2 + CVD risk factors)	-0.15	-0.24*	-0.07	-0.23*
Model 4 (Model 3 + antidepressant use)	-0.11	-0.12	0.05	-0.15

Abbreviations: HRV: heart rate variability; BDI: Beck depression inventory; ULF: ultra-low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency; CVD: cardiovascular disease; CAD: coronary heart disease; BMI: body mass index.

Results are shown as standardized beta-coefficients in linear regression models.

Model 1: base model adjusted for within-pair difference of baseline dependent and independent variable, and between-pair difference of baseline independent variable; **Model 2:** model 1 + confounding factors, including smoking, beta-blocker, education, alcohol, physical activity, prevalent CAD; **Model 3:** model 2 + CVD risk factors, including BMI, hypertension, diabetes; **Model 4:** model 3 + antidepressant use.

* indicates significant association at $p < 0.05$.

eTable 5. Longitudinal association between HRV and current major depressive episode

	visit 1 HRV → visit 2 Depression			
	ULF	VLF	LF	HF
Model 1 (Base model)	-0.36*	-0.37*	-0.33*	-0.34*
Model 2 (Model 1 + confounding factors)	-0.23*	-0.26*	-0.25*	-0.25*
Model 3 (Model 2 + CVD risk factors)	-0.23*	-0.27*	-0.28*	-0.27*
Model 4 (Model 3 + antidepressant use)	-0.22*	-0.22*	-0.20*	-0.20*
	visit 1 Depression → visit 2 HRV			
	ULF	VLF	LF	HF
Model 1 (Base model)	-0.05	-0.27*	-0.14	-0.19*
Model 2 (Model 1 + confounding factors)	-0.03	-0.28*	-0.16*	-0.17*
Model 3 (Model 2 + CVD risk factors)	-0.08	-0.23*	-0.09	-0.15*
Model 4 (Model 3 + antidepressant use)	-0.03	-0.17*	-0.04	-0.11

Abbreviations: HRV: heart rate variability; ULF: ultra-low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency; CVD: cardiovascular disease; CAD: coronary heart disease; BMI: body mass index.

Results are shown as standardized beta-coefficients in linear regression models.

Model 1: base model adjusted for within-pair difference of baseline dependent and independent variable, and between-pair difference of baseline independent variable; **Model 2:** model 1 + confounding factors, including smoking, beta-blocker, education, alcohol, physical activity, prevalent CAD; **Model 3:** model 2 + CVD risk factors, including BMI, hypertension, diabetes; **Model 4:** model 3 + antidepressant use.

* indicates significant association at $p < 0.05$.