The Association between Heart Rate Variability and Cognitive Impairment in Middle-Aged Men and Women. The Whitehall II Cohort Study.

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Abstract

Background: To examine the relationship between reduced heart rate variability (HRV) and cognitive function in middle aged adults in the general population

Methods: HRV, in both time and frequency domains, and cognitive function were measured twice, at mean ages 55 and 61 years, in 5,375 male and female participants of the UK Whitehall II study. Logistic regression was used to model associations between HRV and cognition (short-term verbal memory, reasoning (AH4-I), vocabulary, phonemic and semantic fluency). Cross-sectional associations were assessed at both waves and longitudinal associations as change in cognition over the 5 year follow-up.

Results: No consistent associations were found in men or women, either in cross-section, prospective or the longitudinal analysis of decline in cognition.

Conclusion: Reduced cardiovascular autonomic function does not contribute to cognitive impairment in this middle-aged population. Further studies are needed to verify the potential role of HRV measures in predicting the degeneration of cognitive function at older ages.

INTRODUCTION

Increases in life expectancy make cognitive function an important health outcome. Poor cognitive functioning among adults is not only linked to dementia [1,2] and mortality,[3,4,5] but has also been shown to be associated with some degree of functional impairment.[6] It is important, therefore, to explore the possible predictors of cognitive impairment in order to target better the preventive strategies and public health messages.

Existing research reveals that there are multiple determinants of cognitive decline. Besides age, other factors widely implicated in cognitive decline are pathology, socio-economic factors,[7] vascular disease and risk factors (such as hypertension, diabetes mellitus, cholesterol level, fibrinogen level),[8,9,10] and lifestyle behavioral factors.[11,12] The association between cardiovascular autonomic function and cognitive function is less well explored, although there are several plausible pathways through which the two may be linked, for example via coronary heart disease [13,14], vascular disease, hypertension,[15] immune dysfunction/inflammation [16] and others.[17]

Heart rate variability (HRV) is a noninvasive measure of autonomic input to heart rate that has been successfully used to estimate modulation of autonomic tone. HRV is determined by the interaction of cardiac sympathetic and parasympathetic activity, which causes changes in the beat-to-beat intervals and changes in the frequency components of the heart rate. Short term variations in the beat-to-beat interval (measured as the Standard Deviation in Normal-to-Normal intervals; SDNN) are reduced by decreased parasympathetic activity or sympathetic over stimulation. Low

frequency (LF) power (typically 0.04-0.15 Hz) reflects a combination of both parasympathetic and sympathetic heart rate modulations. Low HRV predicts coronary disease incidence,[18] worse prognosis [19,20,21] and is linked to risk factors for cognitive impairment, such as high cholesterol, raised blood pressure, and raised cortisol. [17,22,23]

To date, there has been very little research, and the findings mixed, as to whether low HRV is associated with cognitive impairment or dementia.[24, 25] The aim of this study, therefore, is to explore the association between reduced HRV and poor cognitive function among middle aged men and women in a general population setting. We examine the cross-sectional, prospective and longitudinal association by examining the association between change in HRV with cognitive decline over a five year period.

METHODS

The Whitehall II study was established in 1985 as a longitudinal population-based study to examine the socioeconomic gradient in health and disease among 10,308 civil servants, then aged 35-55 years.[26, 27] At the fifth and seventh phases of data collection (1997-99 and 2002-4 respectively) all study participants known to be alive and in the country were invited to a screening clinic. Completed cognitive function tests were available on 6073 participants at phase 5 (93% of those attending) and 6370 at phase 7 (98% of those attending). Because of the lack of availability of clinic staff, HRV recordings were not performed on all days during screening. HRV recordings were therefore available on 3365 participants at phase 5 (51% of those attending) and 4095 at phase 7 63% of those attending) of whom 3253 (97%) at Phase 5 and 4033 (98%) at Phase 7 also had cognitive function measures available. A total of 5,375 participants (3809 men and 1566 women) had either cross-sectional or longitudinal data on HRV and cognitive function available and this sample forms the basis for the analyses. The number of participants in each analysis varies according to data availability. The University College London ethics committee approved the study.

Measures of HRV – phases 5 and 7

5-minute supine resting 12-lead electrocardiagrams were obtained using SEER MC recorders (GE Medical Systems, Milwaukee, Wisconsin, USA). The recorders were programmed to capture individual 10 second electrocardiograms every 10 seconds. Five minutes of beat-to-beat heart rate data were re-sampled at 500 Hz frequency in order to obtain digitised sequence of R waves. HRV was analysed both in the time domain (SDNN) and in the frequency domain using the autoregressive method (Blackman-Tukey algorithm). Frequency domain components were computed by

integrating the power spectrum within two frequency bands; 0.04-0.15Hz (Low Frequency power LF, in ms^2) and 0.15-0.4Hz (High Frequency power HF, in ms^2). All the calculations were performed using in-house written software.

Measures of cognitive function – phases 5 and 7

Cognitive function was assessed with a battery of five standard tasks, chosen to provide a comprehensive evaluation of cognitive functioning in middle-aged adults. Cognitive tests were administered to each participant in the screening clinic using a tape recorder. The first test was a 20-word free recall test of short-term verbal memory. Participants were presented a list of 20 one or two syllable words at 2 second intervals and were then asked to recall in writing as many of the words in any order and had 2 minutes to do so.[12] The AH4-I (Alice-Heim 4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty.[28] It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. Participants had 10 min to do this section. The Mill Hill Vocabulary test is a test of verbal meaning and encompasses the ability to recognize and comprehend words.[29] We used the test in its multiple format, consisting of a list of 33 stimulus words ordered by increasing difficulty and six response choices. We used two measures of verbal fluency: phonemic and semantic. [30] Phonemic fluency was assessed via "S" words and semantic fluency via "animal" words. Subjects were asked to recall in writing as many words beginning with "S" and as many animal names as they could. One minute was allowed for each test.

Statistical analyses

SDNN, LF power, and HF power were transformed by natural logarithm because their distributions were skewed. The association between a standard deviation decrease in each HRV parameter and each cognitive function test was estimated using multiple logistic regression analyses. Poor cognitive function was indicated by being in the worst (sex specific) quintile for each test.

We examined these relationships cross-sectionally at two time points (phase 5 and phase 7) and prospectively (phase 5 HRV and phase 7 cognitive function). We also examined the association between HRV at Phase 5 and cognitive decline over 5 years follow-up. These latter analyses were adjusted for the time interval between the two phases. Cognitive decline was defined as being in the worst quintile of change and corresponded to a decrease of 2 or more words (3 or more for women) for memory, 8 or more points on the AH4-I, 2 or more words on the Mill-Hill and 4 or more words on both the phonemic and semantic fluency respectively. All analyses were carried out separately for men and women, but as no gender differences were found, the combined results are presented. Adjustments were made for age, sex and highest educational attainment.

In sensitivity analyses we explored whether HRV and cognitive function were associated in two sub-groups of participants; one group with hypertension (classified as systolic and diastolic blood pressure > 140/90 mm/Hg or treatment for hypertension at Phase 5) and one group with prevalent coronary heart disease (defined as angina or myocardial infarction at any previous phase).

RESULTS

Characteristics of participants in these analyses are shown in table 1. Apart from memory, cognitive scores were equal or lower in women than men and in general the scores were lower at Phase 7. The cross sectional associations, at Phase 5 and Phase 7, between the HRV measures and the five cognitive tests are shown in table 2. At phase 5, LF HRV was negatively associated with memory, the Mill Hill and phonemic and semantic fluency. For instance, one standard deviation decrease in LF was associated with greater odds of poor verbal memory (Odds Ratio (OR) =1.14; 95% confidence interval (CI) = 1.02-1.26). There was generally less evidence of an association between HRV and poor cognitive function at phase 7.

Table 3 presents the prospective association between HRV at Phase 5 and cognitive impairment at Phase 7; there was little evidence of an association. The association between HRV at Phase 5 and cognitive decline between Phase 5 and 7 is shown in Table 4. There was some evidence to suggest that lower HRV was associated with an increased likelihood of being in the worst quintile of change in the Mill-Hill test. No other statistically significant associations were found.

We carried out further analysis in a sub-group of participants with hypertension and there was no evidence of an association between HRV and cognition (data not shown). In the relatively small sub-group of participants with prevalent CHD there was a suggestion that the effects were stronger (Tables 5 and 6).

DISCUSSION

This study of middle aged adults suggests that low HRV is not consistently related to poor cognitive function. This finding supports an earlier case-control study in which 39 individuals with mild cognitive impairment were found to have similar HRV to controls.[31] However, in a cross-sectional analysis of 311 older disabled women, Kim *et al* reported that cardiac autonomic dysfunction, particularly low HF power, was associated with 6.7 times greater odds of cognitive impairment.[32] Our analysis is on a relatively healthy general population sample and there appears to be little evidence of an association between HRV and cognition in middle age.

Dementia occurs late in life but it is increasingly recognized that there is a long preclinical phase characterized by progressive neuropathological changes that then become clinically detectable as cognitive impairment or dementia. The "life-long" view of dementia stresses the importance of risk factors in midlife.[33] One of the problems with examining risk factors in middle age is the lack of standard criteria to judge poor cognitive performance and to assign its clinical significance. Recent attempts to identify poor performance as being in the worst quintile [34] provide appealing solutions to the problem. In addition to the results reported here we also examined this association using linear regression; the results were no different. Our findings on individuals aged 55 and 61 years at the two phases of data collection suggest that low HRV is not a major risk factor at this point in the lifecourse.

Previous studies have been on individuals with Alzheimer's disease and vascular dementia, making it difficult to separate cause and effect. Alzheimer's disease patients have decreased parasympathetic tone which can cause reduced HRV.[32] Allen *et al*

found no difference in HRV measures between those with Alzheimer's disease or dementia and control patients.[35] In contrast, Murakami *et al* report that LF and LF/HF ratio were significantly lower in a group with dementia than normal control group, among individuals aged 75 years and older.[36] We used five tests in order to examine several cognitive dimensions; low HRV was not associated consistently with any test. The cross-sectional and longitudinal analysis showed some association but not with the same cognitive domain, leading to the conclusion that there is no real association between HRV and cognition in our data. Given these mixed findings, further research is clearly needed.

One possible pathway which may link HRV to cognitive function is through increased blood pressure [24] but we found no evidence of an association among a group of our participants with hypertension. HRV is linked to heart disease and there is some evidence to suggest that heart disease is associated with impaired cognition.[13,14] It is plausible, therefore, that associations between reduced cardiac autonomic function and impaired cognition may only be present among those with prevalent coronary heart disease. In a sub-group of our participants with angina or myocardial infarction, there was a suggestion of a stronger relationship between HRV and cognitive function (in particular memory and AH-4). This warrants further investigation in a larger group of people with coronary disease.

There are a number of potential limitations to this study. First, Whitehall II is a study on individuals in stable Civil Service white-collar jobs at baseline and thus does not represent the general population, particularly the lowest end of the socioeconomic spectrum, the unemployed or those in insecure jobs. Thus, further research is needed

to determine the generalisability of our findings. Second, data here are drawn from the 5th and 7th phases of the study, implying both survival and selection effects. Therefore, it is possible that the association between HRV and cognition is underestimated in our sample. Since the Whitehall II study collected only 5-minute short-term electrocardiograms, we were not able to investigate recently proposed advanced methods for HRV assessment that appear to be capable of differentiating sympathetic and vagal influences in long-term electrocardiograms [37]. It is possible that more sophisticated measurements of heart rate variability may have provided different results. Finally, the Whitehall II cognitive test battery does not assess executive functions in detail. It is also possible that additional neuropsychological testing would have shown effects not evident in the tests included in our analysis.

In conclusion, our results show low HRV is not consistently associated with aspects of poor cognitive function in this middle aged sample of men and women. On-going follow-up and further testing as the study participants' age will verify the potential role of HRV measures in predicting the degeneration of cognitive function at older ages.

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Author Contributions:

All authors designed the study, were involved in data acquisition and prepared the text. Dr. Britton wrote the first draft. Mr Shipley was primarily responsible for statistical analyses. Professor Marmot is responsible for quality assurance and control.

There are no conflicts of interest

Table 1: Sample characteristics of participants

	Phase 5 (1997-1999)		Phase 7 (2002-2004)	
	Men	Women	Men	Women
N	3248	1255	3190	1201
Age (mean (SD))	55.5 (6.0)	55.8 (6.0)	60.9 (5.9)	61.0 (6.0)
Heart rate variability (mean (SD)[+])				
SDNN	34.3 (0.44)	32.5 (0.44)	33.7 (0.49)	34.5 (0.47)
LF	326.7 (0.99)	243.9 (0.96)	290.2 (1.07)	270.3 (1.04)
HF	117.0 (1.12)	141.5 (1.15)	107.8 (1.25)	146.3 (1.17)
Cognitive function (mean (SD))				
Memory	6.9 (2.3)	7.0 (2.7)	6.8 (2.3)	7.0 (2.7)
AH4	49.0 (9.7)	42.4 (11.8)	46.3 (9.9)	40.2 (11.8)
Mill-Hill	25.9 (3.7)	23.4 (5.4)	25.8 (3.7)	23.8 (5.3)
Phonemic	17.1 (4.2)	16.7 (4.8)	16.0 (4.0)	15.7 (4.4)
Semantic	16.7 (4.0)	16.0 (4.7)	16.0 (3.7)	15.3 (4.4)

[+] For HRV measures, geometric means are presented with SD of the logged values

Table 2. Cross sectional associations between HRV (1 SD decrease) and cognitive function (odds of lowest quintile).

PHASE 5	Memory		AH4		Mill Hill		Phonemic		Semantic	
1 SD decline in HRV	OR[+]	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N=3029 (2162 men, 847 women)										
SDNN	1.08	0.97-1.20	1.03	0.93-1.14	1.03	0.94-1.14	**1.15**	**1.04-1.26**	1.07	0.97-1.18
HF	1.03	0.93-1.14	1.00	0.91-1.11	1.00	0.91-1.10	1.09	0.99-1.20	1.05	0.95-1.16
LF	**1.14**	**1.02-1.26**	1.08	0.98-1.20	**1.10**	**1.00-1.21**	**1.15**	**1.04-1.26**	**1.11**	**1.01-1.23**
PHASE 7	Memory		AH4		Mill Hill		Phonemic		Semantic	
1 SD decline in HRV	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N=3569 (2605 men, 964 women)										
SDNN	0.95	0.87-1.05	0.93	0.85-1.02	0.98	0.90-1.07	1.00	0.92-1.10	**1.12**	**1.02-1.24**
HF	0.94	0.86-1.03	**0.87**	**0.80-0.95**	0.97	0.89-1.06	0.97	0.89-1.07	1.04	0.94-1.14
LF	0.95	0.87-1.05	0.95	0.87-1.05	1.03	0.94-1.12	1.01	0.92-1.10	**1.14**	**1.04-1.25**

[+] Odds ratios are adjusted for age, sex and highest educational attainment

Table 3. Prospective association between HRV at phase 5 (1 SD decrease) and cognitive function at phase 7 (odds of lowest quintile).

	Memory		AH4		Mill Hill		Phonemic		Semantic	
1 SD decline in HRV	OR[+]	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N=2669 (1937 men, 732 women)										
SDNN	1.01	0.90-1.12	1.03	0.93-1.15	1.02	0.91-1.13	1.10	0.99-1.22	1.07	0.96-1.18
HF	0.98	0.88-1.10	1.00	0.90-1.12	1.01	0.91-1.13	1.06	0.94-1.18	1.00	0.90-1.12
LF	1.05	0.94-1.18	1.05	0.94-1.18	1.05	0.94-1.17	1.09	0.98-1.22	1.09	0.97-1.21

[+] Odds ratios are adjusted for age, sex and highest educational attainment

Table 4. Prospective association between HRV at phase 5 (1 SD decrease) and decline in cognitive function between Phase 5 and Phase 7 (odds of lowest quintile of change).

	Memory		AH4		Mill Hill		Phonemic		Semantic	
1 SD decline in HRV	OR[+]	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N=2595 (1883 men, 712 women)										
SDNN	1.02	0.92-1.12	1.05	0.95-1.17	**1.16**	**1.05-1.29**	0.97	0.88-1.07	0.94	0.85-1.05
HF	1.01	0.91-1.11	1.01	0.91-1.12	**1.18**	**1.06-1.31**	0.96	0.87-1.06	0.90	0.81-1.00
LF	1.06	0.96-1.18	1.04	0.93-1.15	**1.19**	**1.08-1.32**	0.98	0.88-1.08	0.95	0.86-1.06

[+] Odds ratios are adjusted for age, sex and highest educational attainment and time interval between Phase 5 and Phase 7

Table 5. Cross sectional associations between HRV (1 SD decrease) and cognitive function (odds of lowest quintile) among participants with coronary heart disease.

PHASE 5	Memory		AH4		Mill Hill		Phonemic		Semantic	
1 SD decline in HRV	OR[+]	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N=211 (115 men, 56 women)										
SDNN	1.23	0.85-1.77	**1.56**	**1.10-2.23**	1.13	0.79-1.62	1.10	0.78-1.54	1.27	0.91-1.78
HF	1.26	0.88-1.80	1.27	0.92-1.76	0.97	0.69-1.36	1.16	0.84-1.60	1.07	0.78-1.48
LF	**1.55**	**1.05-2.29**	**1.59**	**1.09-2.31**	1.26	0.87-1.83	1.09	0.77-1.55	1.31	0.92-1.85
PHASE 7	Memory		AH4		Mill Hill		Phonemic		Semantic	
1 SD decline in HRV	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N= 353 (272 men, 81 women)										
SDNN	0.94	0.74-1.19	1.05	0.82-1.34	0.94	0.73-1.20	1.12	0.86-1.45	1.26	0.97-1.64
HF	1.01	0.79-1.29	0.94	0.73-1.20	0.91	0.71-1.17	1.09	0.83-1.42	1.11	0.86-1.43
LF	0.87	0.68-1.12	1.04	0.81-1.34	0.95	0.74-1.23	1.14	0.87-1.49	1.19	0.91-1.54

[+] Odds ratios are adjusted for age, sex and highest educational attainment

Table 6. Prospective association between HRV at phase 5 (1 SD decrease) and cognitive function at phase 7 (odds of lowest quintile) among participants with coronary heart disease.

	Memory		AH4		Mill Hill		Phonemic		Semantic	
1 SD decline in HRV	OR[+]	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N= 181 (132 men, 49 women)										
SDNN	0.84	0.58-1.23	1.25	0.84-1.86	1.06	0.68-1.66	1.04	0.72-1.50	0.97	0.67-1.41
HF	0.83	0.58-1.18	1.01	0.69-1.48	0.99	0.64-1.52	1.00	0.70-1.43	0.95	0.66-1.36
LF	0.98	0.66-1.46	1.45	0.95-2.20	1.27	0.81-1.99	1.11	0.75-1.63	1.18	0.79-1.75

[+] Odds ratios are adjusted for age, sex and highest educational attainment and time interval between Phase 5 and Phase 7

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