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Shift work is associated with reduced heart rate variability among men but not women

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A B S T R A C T

Background: Imbalance in the autonomic nervous system due to a disrupted circadian rhythm may be a cause of shift work-related cardiovascular diseases.
Objective: We aimed to determine the association between shift work and cardiac autonomic activity in blue-collar workers.
Methods: The study included 665 blue-collar workers aged 18–68 years in different occupations from two Danish cohort studies. Time and frequency domain parameters of heart rate variability (HRV) were measured during sleep using the Actiheart monitor, and used as markers of cardiac autonomic function. Multiple linear regression analyses were used to investigate differences in HRV between day and shift workers.
Results: Shift workers had no significantly different HRV parameters than day workers, except for a lower VLF (B: 0.21; 95% CI: −0.36–0.05). The lower VLF was only present among non-night shift workers ($p < 0.05$) and not among night shift workers ($p > 0.05$). Results differed significantly by gender (p for interaction < 0.10): among men, shift work was negatively associated with RMSSD (B: −7.83; 95% CI: −14.28–1.38), SDNN (B: −7.0; 95% CI: −12.27–1.78), VLF (B: −0.27; 95% CI: −0.46–0.09) and Total Power (B: −0.61; 95% CI: −1.20–0.03), while among women, shift work was only associated with the LF/HF ratio (B: −0.29; 95% CI: −0.54–0.03).
Conclusion: Shift work was particularly associated with lower HRV during sleep among men. This indicates that shift work causes imbalance in the autonomic nervous system among men, which might increase their risk of cardiovascular diseases.

1. Introduction

More than twenty percent of the working population in the European Union reports working shifts [1], and this will further increase as the societal demand for the provision of goods grows [2,3]. Reviews and meta-analyses show that working in rotating shifts, and even more when night shifts are included, increases the risk of chronic diseases, such as type 2 diabetes [4–7] and cardiovascular diseases (CVD) [8,9].

Evidence suggests different interrelated pathways of shift work leading to CVD [9–11]. Working in shifts may lead to behavioral changes, such as smoking, a poor diet, and less physical activity, which increases the risk of CVD [10,12]. Another theory is that shift work leads to desynchronization of the circadian rhythm and biological clock [10]. Hereby, the ability of the cardiovascular system to adapt to external influences decreases, which results in tissue damage and an increased risk of CVD [12,13]. A third theory suggests that disruption of the circadian rhythm due to shift work to cause imbalanced autonomic regulation of the cardiovascular system [14,15]. Autonomic imbalance is an established risk factor for CVD and can be measured by heart rate variability (HRV), the variation in time interval between successive heartbeats [16]. A low HRV at rest is associated with an increased risk of 32–45% for a first cardiovascular event [17]. It is also associated with poor general health status and greater cardiovascular morbidity and mortality [14,15].

The systematic review of Togo et al. showed inconsistent results in the relation between shift work and HRV during rest or work across relatively small studies (n = 6–240) [9]. More recent studies suggested that working in rotating night shifts is adversely related to HRV [13,18–20].

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However, three of the four studies included only male shift workers and did not compare shift workers to day workers [13,18,20], which is optimal to examine the long-term chronic effects of shift work. Kunikullaya et al. compared day workers with night shift workers and showed a trend towards an increased sympathetic activity among night shift workers, but did not find statistically significant differences [19]. Moreover, none of the previous studies distinguished between night shift workers and non-night shift workers [13,18–20], nor investigated differences by age and gender [13,18–20]. This is significant because research has shown that HRV largely depends on age and gender [21,22].

The aim of this study was to determine the association between shift work (with and without night shifts) and cardiac autonomic activity during sleep in blue-collar workers, and to investigate differences by age and gender. We hypothesized that shift workers, particularly those with night shifts, have lower HRV during sleep than day workers.

2. Methods

2.1. Population

Cross-sectional data were used from two Danish cohort studies: the New method for Objective Measurements of physical Activity in Daily living (NOMAD) and the Danish Physical ACTivity cohort with Objective measurements (DPhacto) [23,24]. In the NOMAD study, 358 blue-collar workers from 7 Danish workplaces were invited to participate in the study, all primarily recruited via contact with trade unions and safety representatives. The workers were aged 18–65 years and data collection was conducted between October 2011 and April 2012. In DPhacto, 2107 blue-collar workers from 15 different workplaces were invited. Workers were aged 18–68 years and data collection took place between April 2012 and May 2013. Details of the study designs have been described elsewhere [23,24]. Exclusion criteria for the present study were being white-collar worker, working less than 20 h/week, occupations in which nobody works in irregular shifts, pregnancy, pacemaker, history of CVD, allergy to adhesive tape, reporting fever, and missing data on shift work, HRV or covariates. All workers gave written informed consent prior to the study and the regional Ethics Committee in Copenhagen, Denmark (journal number H-2-2011-047 and H-2-2012-011).

2.2. Variables

2.2.1. Shift work

In both NOMAD and DPhacto, workers were asked about their shift work using a question: "At which time of the day do you usually work in your main occupation?". This is a validated question used by the National Research Center for the Working Environment in Denmark in their National working environment and health questionnaire in 2012 [25]. In the NOMAD study, the response options were "fixed day work", "fixed evening work (mostly between 15:00 and 24:00)", "fixed night work (mostly between 24:00 and 05:00 h)", "varying working hours with night shifts", "varying working hours without night shifts", and "other". In the DPhacto study, response options were "day work", "night or varying working hours with night shifts", and 'other'. In line with our previous study [26], data from both studies were merged into day work and shift work, subdivided into night shift work (i.e. workers with fixed and/or varying night shifts) and non-night shift work (i.e. shift workers without night shifts).

2.2.2. HRV

Objective data on HRV were collected for four consecutive days, during 24 h per day using the Actiheart monitor [23,24]. This is a small and water resistant device for recordings over multiple days [27]. Measurement of HRV using the Actiheart was found technically reliable and valid when compared to state-of-the art clinical measurements (Holter monitoring) [27]. According to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [16], non-overlapping five-minute windows were used to measure inter-beat-interval (IBIs). HRV parameters in both the time and frequency domains were derived from these IBIs. The calculated time domains were: the Standard Deviation of Normal to Normal IBIs (SDNN) and the Root Mean Square of Successive Differences (RMSSD). The four calculated frequency domain parameters were: very low-frequency spectral power (VLF: 0.003–0.04 Hz), low-frequency spectral power (LF: 0.04–0.15 Hz), high-frequency spectral power (HF: 0.15–0.4), and the ratio between low- and high-frequency components (LF/HF ratio) [23]. Total power was calculated by the sum of VLF, LF, and HF. SDNN and Total Power are expressions of global HRV; RMSSD and HF reflect parasympathetic cardiac activity; LF is considered as a quantitative marker for sympathetic modulations, but is also as a reflection of both sympathetic and parasympathetic activity; LF/HF is an indicator of sympathetic-to-parasympathetic balance; and VLF possibly reflects sympathetic function though its physiological origin is controversial [16,28,29].

In the present study, HRV during sleep was analyzed to assess the autonomic nervous system at rest, using the three five-minute intervals in which the highest average IBIs (lowest heart rate) were detected. This could occur at any time of the day and was detected by the combination of data from the diary (sleep times) and accelerometer (Actigraph GT3X+). In line with the study of Hallman et al. [23], we applied the following cleaning criteria for HRV measurement during sleep: 1) data from the first 30 and last 15 min were removed to avoid transient periods, such as falling asleep or waking up; 2) intervals for which trunk movement occurred or the posture was not classified as "lying" were removed; and 3) periods where the percentage of erroneous IBIs was higher than 5% were removed.

2.3. Covariates

Workers completed a questionnaire at baseline on sociodemographic and lifestyle factors. Smoking status was dichotomized into current smoker (yes daily/yes sometimes) and non-smoker (no/former smoker). Alcohol use was dichotomized into none/moderate drinker (i.e. ≤1 drink/day for women and ≤2 drinks/day for men) and heavy drinker [30]. Present occupational sector was categorized into: cleaning, manufacturing, transportation, and other (i.e. health services, assemblers, and garbage collectors). Working hours was asked by "how many hours per week do you work in your main occupation, including extra hours?" (continuous). Furthermore, objectively measured body weight and body height were used to calculate BMI in kg/m^2 (continuous). Data on occupational physical activity and leisure-time physical activity (percentage time spent in moderate-to-vigorous physical activity) were collected from accelerometer recordings using the Actigraph GT3X as described elsewhere [26].

2.4. Data analysis

Multiple linear regression models were fitted to estimate regression coefficients for the association between shift work and HRV parameters. Gender, age, BMI, smoking, alcohol and objectively measured physical activity at work and leisure time were included in the models as potential confounders based on literature [15,21]. We tested whether inclusion of occupational sector and working hours changed the regression coefficient of the crude models by ≥10% [31]. As this was not the case, we did not include them as covariates in the models. The independent variable was shift work (shift work with and without night shifts versus day work) and the dependent outcome variables were HRV parameters: IBI, RMSSD, SDNN, VLF, LF, HF, LF/HF, and Total Power. VLF, LF, HF, LF/HF ratio as well as Total Power were log-transformed because the residuals did not follow a normal distribution. In additional analyses, shift work status was categorized into three categories (day work, night shift work, and non-night shift work) to investigate whether HRV parameters of night shift workers were more affected than those of non-night shift workers. Age and gender were a priori selected as potential effect modifiers and tested in the primary models [21,22]. Due to limited statistical power for testing interaction effects, we considered an interaction term between shift work and age or gender as statistically significant if $p < 0.10$. If significant, stratified analyses were carried out. Analyses were carried out using SPSS version 22, and a two-sided p-value smaller than 0.05 was considered statistically significant.

3. Results

3.1. Participants

Of the 1355 participating workers, we excluded 215 white-collar workers, 27 workers who worked less than 20 h per week, 56 who worked in an occupational sector without shift workers, eight with a history of CVD, two with a pacemaker, 51 workers with missing values on shift work or covariates, and 331 workers without valid HRV measurements (Suppl. Fig. 1). Baseline characteristics of workers with and without valid HRV measurement were comparable (data not shown). This led to a study population of 543 day workers and 122 shift workers, consisting of 74 night shift workers and 48 non-night shift workers.

Of the 665 blue-collar workers, 56.1% were male, 30.4% reported being a smoker, and 18.5% being a heavy drinker (Table 1). Compared to day workers, night shift workers were statistically significantly more often male, worked less often in cleaning, and more in transportation and manufacturing. Non-night shift workers were statistically significantly more often smokers and worked more in cleaning and transportation than day workers. Means and standard deviations for HRV parameters during sleep are presented in Table 2.

3.2. Association between shift work and HRV during sleep

The linear regression models adjusted for age, gender, BMI, smoking, and alcohol showed that shift work was not associated with HRV parameters, except for ln VLF (B: −0.21; 95% CI: −0.36–0.05) (Table 3). This means that VLF is 23% lower in shift workers than in day workers (formula: $100 * (\text{Exp}(B) - 1)\%$). Non-night shift workers

Table 1
Baseline characteristics of the blue-collar workers by shift work status.

	Day workers	Night shift workers	Non-night shift workers
	n = 543	n = 74	n = 48
Demographics			
Age (years)	45.7 ± 10.0	45.4 ± 9.7	44.8 ± 9.7
Gender (male)	292 (54%)	57 (77%)*	24 (50%)
Occupational			
Working hours/week	38 ± 5	39 ± 7	37 ± 6
Occupational sector			
Cleaning	101 (19%)	4 (5%)*	16 (33%)*
Manufacturing	350 (65%)	53 (72%)*	22 (46%)*
Transportation	42 (8%)	16 (22%)*	6 (13%)*
Other	50 (9%)	1 (1%)[b]	4 (8%)[b]
Health and lifestyle			
Smoker	160 (30%)	21 (28%)	21 (44%)*
Alcohol (units per week)	4.0 ± 5.5	5.3 ± 9.01	3.7 ± 5.6
Heavy drinker	95 (18%)	18 (24%)	10 (21%)
Body mass index (kg/m²)[a]	27.1 ± 4.7	27.2 ± 4.6	27.6 ± 5.5
Overweight	226 (42%)	26 (35%)	16 (33%)
Obesity	122 (23%)	20 (27%)	15 (31%)
Moderate-to-vigorous physical activity work (h/day)[a]	1.2 ± 0.6	1.1 ± 0.5	1.1 ± 0.5
Moderate-to-vigorous physical activity leisure (h/day)[a]	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.3

Values represent means ± standard deviations or numbers and (percentages).
* Statistically significant difference ($p < 0.05$) tested with the two-sample t-test and chi-square test between night shift workers, non-night shift workers and day workers (reference).
[a] Objectively measured using the Actigraph GT3X accelerometer.
[b] Could not be statistically tested due to the low number of participants in each cell.

had a significantly lower ln VLF (B: −0.32; 95% CI: −0.55–0.09) than day workers, while ln VLF did not differ between non-night shift workers and day workers (B: −0.13; 95% CI: −0.32–0.06).

3.2.1. Gender differences

There was no effect modification by age (all p-values for interaction > 0.10). The interaction terms between gender and shift work were statistically significant for IBI, RMSSD, SDNN, HF, and LF/HF ratio (p = 0.058, 0.046, 0.062, 0.047, 0.073, respectively). These interaction terms remained statistically significant after adjustment for occupational sector and smoking status. Table 4 shows that male shift workers had significantly lower SDNN (B: −7.03; 95% CI: −12.27–1.78), RMSSD (B: −7.83; 95% CI: −14.28–1.38), ln VLF (B: −0.27; 95% CI: −0.46–0.09), and ln Total Power (B: −0.61; 95% CI: −1.20–0.03) than male day workers. Among women, shift workers had a significantly lower ln LF/HF ratio (B: −0.29; 95% CI: −0.54–0.03) than day workers.

4. Discussion

In the total study population of blue collar workers, shift work was not significantly associated with HRV parameters during sleep, except for VLF. Compared to day workers, VLF appeared to be lower in non-night shift workers but not in night workers. However, among men, shift workers had a significantly lower SDNN, RMSSD, VLF and Total Power than day workers. These HRV parameters reflect decreased function of sympathetic, parasympathetic, and overall components of the autonomic nervous system [16,28,29]. This can be interpreted as weakened ability of the autonomic nervous system to adapt to internal and external environmental challenges, lowered coping ability to emotional/physical stressors, which may lead to poor health in general [29]. Among women, shift work was associated with lower LF/HF ratio only. Although the LF/HF ratio has been questioned as an indicator of sympathetic-parasympathetic balance [32], our finding suggests less predominance of sympathetic cardiac modulations and enhanced overall autonomic balance in favor of parasympathetic activity in shift working women than in day working women.

The present study extended previous research by investigating the association for both night shift work and non-night shift work with HRV under natural – i.e. not artificial - conditions during sleep in male and female workers. Our results did not confirm our hypothesis that shift workers, particularly those with night shifts, have lower HRV than day workers. It is likely that the observed associations between shift work and HRV parameters in men were not observed in the total population because of the absence of associations among women. To the best of our knowledge, only one previous study included both genders comprising 11 male and 25 female night shift workers [19]. They reported no significant difference in HRV between night shift workers and day workers, which is in line with our results in the total population showing that HRV during sleep of night shift workers did not differ from that of day workers. In non-night shift workers, we found only VLF to be statistically significantly different between shift and day workers. This result reflects reduced overall activity of various slow mechanisms of sympathetic function, such as thermoregulatory mechanisms, fluctuation in activity of renin-angiotensin system, and the function of peripheral chemoreceptors, in non-night shift workers [33,34]. However, the exact physiological interpretation of VLF is unclear [16]. In addition, noise signals typically present in 5 minute

Table 2
Mean and standard deviations (SD) of heart rate variability (HRV) during sleep in blue-collar workers, stratified by gender (n = 665).

	Men			Women		
	Day worker	Night shift worker	Non-night shift worker	Day worker	Night shift worker	Non-night shift worker
	n = 292	n = 57	n = 24	n = 251	n = 17	n = 24
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
IBI (ms)	1113 (141)	1082 (133)	1075 (112)	1035 (129)	1129 (195)	1006 (138)
RMSSD (ms)	52 (31)	45 (25)	43 (32)	49 (28)	60 (26)	49 (22)
SDNN (ms)	60 (23)	53 (22)	50 (25)	53 (23)	59 (21)	52 (17)
VLF (ms²/Hz)	1047 (815)	816 (596)	732 (806)	880 (862)	941 (686)	588 (369)
ln VLF ln(ms²/Hz)	6.6 (0.9)	6.5 (0.7)	6.2 (0.9)	6.4 (0.8)	6.5 (1.0)	6.2 (0.6)
LF (ms²/Hz)	1113 (1127)	1057 (1009)	762 (763)	840 (1070)	820 (746)	609 (458)
ln LF ln(ms²/Hz)	6.6 (0.9)	6.6 (0.9)	6.2 (1.0)	6.2 (1.0)	6.3 (1.0)	6.2 (0.7)
HF (ms²/Hz)	1101 (1583)	1057 (1008)	973 (1836)	1005 (1301)	1213 (848)	832 (630)
ln HF ln(ms²/Hz)	0.4 (1.0)	6.1 (1.2)	6.0 (1.3)	6.3 (1.1)	6.8 (0.8)	6.4 (0.8)
LF/HF ratio	2.5 (3.2)	2.4 (2.1)	1.7 (1.7)	1.4 (1.2)	1.0 (1.3)	1.2 (1.0)
ln LF/HF ratio	0.44 (0.99)	0.58 (0.78)	0.21 (0.82)	0.02 (0.79)	−0.49 (0.89)	−0.14 (0.75)
Total Power (ms²/Hz)	3262 (2889)	2713 (2194)	2467 (2856)	2725 (2795)	2975 (1847)	2030 (1139)
ln Total Power ln(ms²/Hz)	19.6 (2.6)	19.1 (2.6)	18.5 (2.8)	19.0 (2.6)	19.6 (2.3)	18.8 (1.7)

Abbreviation: IBI, inter-beat-interval; SDNN, Standard Deviation of Normal to Normal IBIs; RMSSD, Root Mean Square of Successive Differences; VLF, very low-frequency spectral power; LF, low-frequency spectral power; HF, high-frequency spectral power; LF/HF, ratio between LF and HF components; Total Power, the sum of VLF, LF and HF.

Table 3
Crude and adjusted regression models investigating the association between day and shift work and between day work, night shift work, and non-night shift work and heart rate variability (HRV) during sleep in blue-collar workers (n = 665).

HRV parameters	Shift work (n = 122) vs day work (n = 543)	Night shift work (n = 74) vs day work (n = 543)	Non-night shift work (n = 48) vs day work (n = 543)
	B (95% CI)	B (95% CI)	B (95% CI)
IBI			
Crude	−4.96 (−32.79–22.87)	15.71 (−18.63–50.05)	−36.82 (−78.55–4.91)
Adjusted	−8.69 (−35.08–17.71)	0.60 (−32.19–33.40)	−22.77 (−62.37–16.83)
RMSSD			
Crude	−3.57 (−9.27–2.14)	−2.63 (−9.69–4.43)	−5.02 (−13.60–3.57)
Adjusted	−3.59 (−8.82–1.65)	−2.34 (−8.84–4.16)	−5.47 (−13.32–2.38)
SDNN			
Crude	−3.47 (−8.02–1.08)	−1.89 (−7.52–3.73)	−5.89 (−12.73–0.95)
Adjusted	−3.83 (−8.11–0.44)	−2.74 (−8.05–2.58)	−5.50 (11.91–0.91)
ln VLF			
Crude	**−0.19 (−0.35 to −0.03)**	−0.08 (−0.28–0.11)	**−0.35 (−0.59 to −0.11)**
Adjusted	**−0.21 (−0.36 to −0.05)**	−0.13 (−0.32–0.06)	**−0.32 (−0.55 to −0.09)**
ln LF			
Crude	−0.06 (−0.25–0.13)	0.07 (−0.17–0.30)	−0.26 (−0.54–0.03)
Adjusted	−0.09 (−0.27–0.09)	−0.00 (−0.23–0.22)	−0.22 (−0.48–0.05)
ln HF			
Crude	−0.04 (−0.27–0.19)	−0.03 (−0.32–0.26)	−0.06 (−0.41–0.29)
Adjusted	−0.02 (−0.24–0.19)	0.20 (−0.24–0.28)	−0.09 (−0.41–0.23)
ln LF/HF			
Crude	−0.03 (−0.21–0.15)	0.09 (−0.13–0.31)	−0.21 (−0.48–0.06)
Adjusted	−0.07 (−0.24–0.09)	−0.03 (−0.24–0.17)	−0.14 (−0.39–0.11)
ln Total Power			
Crude	−0.29 (−0.80–0.22)	−0.05 (−0.68–0.58)	−0.66 (−1.43–0.10)
Adjusted	−0.32 (−0.79–0.16)	−0.11 (−0.71–0.48)	−0.625 (−1.34–0.09)

Presented as regression coefficients (95% confidence interval) and p-value, significant associations are shown in bold. Adjusted for age, gender, BMI, smoking, and alcohol. Since additional adjustment for physical activity did not lead to a change of significant parameters and the physical activity variable contained a considerable number of missing values, regression models were presented without adjustment for objectively measured physical activity.
Abbreviation: IBI, inter-beat-interval; SDNN, Standard Deviation of Normal to Normal IBIs; RMSSD, Root Mean Square of Successive Differences; VLF, very low-frequency spectral power; LF, low-frequency spectral power; HF, high-frequency spectral power; LF/HF, ratio between LF and HF components; Total Power, the sum of VLF, LF and HF.

Table 4
Crude and adjusted regression models investigating the association between shift work and heart rate variability (HRV) during sleep by gender (interaction p < 0.1) in blue-collar workers (n = 665).

HRV parameters	Men n = 373	Women n = 292	p-Value for interaction between shift work and gender
	Day workers (n = 292) vs shift workers (n = 81)	Day workers (n = 251) vs shift workers (n = 41)	
	B (95% CI)	B (95% CI)	
IBI			
Crude	−33.20 (−67.31–0.91)	21.50 (−23.52–66.52)	**0.058**
Adjusted	−28.51 (−61.50–4.48)	27.10 (−16.84–71.03)	
RMSSD			
Crude	**−8.03 (−15.41–0.66)**	4.13 (−5.07–13.33)	**0.046**
Adjusted	**−7.83 (−14.28 to −1.38)**	3.62 (−5.25–12.49)	
SDNN			
Crude	**−7.33 (−13.05 to −1.62)**	1.69 (−5.84–9.22)	**0.062**
Adjusted	**−7.03 (−12.27 to −1.78)**	1.69 (−5.65–9.03)	
ln VLF			
Crude	**−0.28 (−0.47 to −0.09)**	−0.10 (−0.38–0.18)	0.285
Adjusted	**−0.27 (−0.46 to −0.09)**	−0.10 (−0.37–0.18)	
ln LF			
Crude	−0.16 (−0.38–0.71)	−0.01 (−0.33–0.30)	0.465
Adjusted	−0.14 (−0.36–0.07)	−0.00 (−0.31–0.31)	
ln HF			
Crude	−0.20 (−0.51–0.11)	0.29 (−0.07–0.65)	**0.047**
Adjusted	−0.20 (−0.46–0.08)	0.28 (−0.06–0.63)	
ln LF/HF			
Crude	0.03 (−0.20–0.27)	**−0.30 (−0.57 to −0.04)**	**0.073**
Adjusted	0.04 (−0.18–0.25)	**−0.29 (−0.54 to −0.03)**	
ln Total Power			
Crude	**−0.64 (−1.28 to −0.00)**	0.18 (−0.67–1.03)	0.131
Adjusted	**−0.61 (−1.20 to −0.03)**	0.18 (−0.64–1.01)	

Presented as regression coefficients (95% confidence interval) and p-value, significant associations are shown in bold. Adjusted for age, gender, BMI, smoking, and alcohol. Since additional adjustment for physical activity did not lead to a change of significant parameters and the physical activity variable contained a considerable number of missing values, regression models were presented without adjustment for objectively measured physical activity.
Abbreviation: IBI, inter-beat-interval; SDNN, Standard Deviation of Normal to Normal IBIs; RMSSD, Root Mean Square of Successive Differences; VLF, very low-frequency spectral power; LF, low-frequency spectral power; HF, high-frequency spectral power; LF/HF, ratio between LF and HF components; Total Power, the sum of VLF, LF and HF.

measurements of VLF may have introduced random measured error [16], although this may be limited as we used the average VLF of three measurement periods each night for four consecutive nights. As reduced VLF has also been associated with an increased risk of CVD and premature mortality [35,36], the finding of reduced VLF in non-night shift workers may be relevant and warrants further investigation.

Importantly, shift work showed adverse associations with multiple HRV parameters among men. This is in line with previous studies [13,18,20] that analyzed male employees with a rotating shift system and found significant differences between the day and night workers. The meta-analysis of Koenig et al. [22] on gender differences in HRV stated that there are substantial gender differences, and that HRV data cannot be treated equally for men and women. However, most studies included only male or female shift workers and were therefore unable to test for gender differences [9,13,18,20]. We showed that shift work is associated with reduced SDNN, RMSSD, Total Power, and VLF during sleep among men, but not women. This is important since reduced SDNN, in particular in combination with reduced RMSSD, has been found to increase the risk of CVD via multiple possible pathways [16,17,28,29]. These pathways include reduced baroreceptor function, reduced endothelial function, elevated blood pressure and excess inflammation. In addition, Total Power reflects similar components of the autonomic nervous system as SDNN, and has also been associated with CVD [37]. Thus, our findings indicate that shift work and the corresponding disruption of circadian rhythms may result in reduced HRV among men, leading to an increased risk of CVD.

The gender differences in the associations between shift work and HRV parameters imply that shift work is differently associated with the autonomic nervous system regulation among men than among women [22]. Parasympathetic activity is, in general, more dominant among women than men [22]. A greater parasympathetic activity is associated with better cardiovascular health, which could explain the cardiovascular health disparity between men and women [22]. Furthermore, differences in working conditions, such as physical workload and working schedule, and potential gender differences in recovery from work may have led to the observed gender difference in the association between shift work and HRV [38]. Thus, our results suggest that underlying mechanisms of shift work leading to CVD might differ between men and women. Based on current evidence, CVD prevention among shift workers should focus on a combination of individual shift scheduling and educational programs for shift workers, including topics such as awareness of the possible consequences of shift work, individual strategies to improve sleep quality, and how to cope with difficulties in the social environment [39,40]. Although our results indicate differences in effect of shift work by gender, it does not provide a basis to organize prevention differently by gender. It is first necessary to further determine the underlying mechanism using prospective studies, investigating the association between both male and female workers and HRV, as well as various shift work features, such as a rotating or fixed system, shift work frequency, and shift work duration.

4.1. Strengths and limitations

The main strength of the present study is the objective measurement of both HRV and sleep in a relatively large homogeneous group of blue-collar workers across multiple days. With the strict criteria for sleep, it was possible to detect sleep that was not affected by arousals, movements and/or poor sleep quality, resulting in a reliable measure to investigate the autonomic nervous system at rest [41,42]. A few limitations of this study should also be noted. Shift work status was measured using a single question, and detailed information on frequency and duration of shift work is lacking. It might therefore be that we were unable to detect associations between shift work and HRV that are only present in shift workers with high exposure to shift work (e.g. high frequency and long duration of shift work). We classified shift workers into day workers, night workers or non-night workers, according to the times of day they usually work. As a result, the association between shift work and HRV can most likely be interpreted as the combination of acute short-term effects of shift work and long-term chronic effects of accumulated exposure to shift work on the autonomic nervous system. It is difficult to differentiate between acute and chronic effects of shift work, but chronic effects largely diminish when comparing HRV after night shifts to HRV after day shifts within the same person. As only 22% of the night shift workers ($n = 16$) actually worked at least one night shift (i.e. working at least 1 h between midnight and 5 am) as well as at least one day shift during the four measurement days, we were unfortunately unable to do this. Furthermore, although we analyzed differences between night shift work and non-night shift work and we were able to show differences by gender, the statistical power was insufficient to further stratify night and non-night shift work by gender. Finally, it is possible that the healthy worker effect introduced selection bias. The healthy worker effect starts with pre-employment selection and continues with a survivor effect in which the less healthy workers are more likely to quit their job [43]. This may have led to an underestimation of the real effect of night shift work on HRV.

4.2. Conclusions

Shift work showed adverse associations for multiple parameters of HRV among men, while shift work appeared to be positively associated with one HRV parameter among women. These results indicate that shift work is associated with imbalanced autonomic nervous system regulation among men, but not among women. Considering that more than 20% of the working population works in shifts [1], these findings stress the need for strategies to promote cardiovascular health among shift workers.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.01.089.

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Declarations of interest

The authors report no relationships that could be construed as a conflict of interest.

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