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ORIGINAL RESEARCH

Shift Work and the Risk of Cardiometabolic Multimorbidity Among Patients With Hypertension: A Prospective Cohort Study of UK Biobank

Liu Yang, MD*; Yi Luo, MD*; Lingfang He, MD; Jinghua Yin, MD; Tie Li, BS; Shuai Liu, MD; Dongjie Li, MD; Xunjie Cheng, MD; Yongping Bai, MD

BACKGROUND: Although the association between shift work and individual cardiometabolic diseases has been well studied, its role in the progression to cardiometabolic multimorbidity (CMM) remains unclear. In this study, we investigate the association between shift work and the incidence of CMM in patients with hypertension.

METHODS AND RESULTS: This study is a population-based and prospective cohort study on 36 939 UK Biobank participants. We used competing risk models to examine the association between shift work and the risk of CMM, which was defined as coexistence of hypertension and diabetes, coronary heart disease, or stroke in our study. We also investigated the association between the frequency and duration of shift work and CMM risks. In addition, we conducted a cross-classification analysis with the combination of frequency and duration of shift work, chronotype and sleep duration as the exposure metrics. During a median follow-up of 11.6 years, a total of 5935 participants developed CMM. We found that usually/always night shift workers were associated with a 16% higher risk of CMM compared with day workers (hazard ratio [HR], 1.16 [95% CI, 1.02–1.31]). We also found that a higher frequency of night shifts (>10/month) was associated with increased risk of CMM (HR, 1.19 [95% CI, 1.06–1.34]) that was more pronounced for >10/month in combination with a morning chronotype or <7 hours or >8 hours of sleep duration (HR, 1.26 [95% CI, 1.02–1.56]; HR, 1.43 [95% CI, 1.19–1.72], respectively).

CONCLUSIONS: We find that night shift work is associated with higher CMM risk in patients with hypertension.

Key Words: biological specimen banks ■ follow-up studies ■ incidence ■ multimorbidity ■ prospective studies ■ shift work schedule

Cardiometabolic multimorbidity (CMM), defined as the coexistence of ≥2 cardiometabolic diseases (CMDs), has become an emerging research priority for public health care professionals.[1] With recent increases in lifespan because of advances in health care, many individuals with a single CMD now have a higher likelihood of developing another, which has resulted in a rapidly rising prevalence of CMM.[2,3] Furthermore, previous studies have reported that the coexistence of hypertension and at least one other chronic condition was most common among patients with multimorbidity.[4] One study showed that the risk of all-cause mortality significantly increased, from 7% to 30%, after the progression of CMM in patients with hypertension.[5] There is also substantial evidence that CMM is related to higher disability and all-cause mortality, lower quality of life, increased health care costs, and reduced the life expectancy.[5–7] Considering the high prevalence and

Correspondence to: Yongping Bai, MD, Department of Geriatric Medicine, Xiangya Hospital, Central South University, Xiangya Road 87#, Changsha 410008, China. Email: baiyongping@csu.edu.cnand Xunjie Cheng, MD, Department of Geriatric Medicine, Xiangya Hospital, Central South University, Xiangya Road 87#, Changsha 410008, China. Email: linqiuyucheng@163.com

*L. Yang and Y. Luo are co-first authors.

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CLINICAL PERSPECTIVE

What Is New?

- Shift work is associated with higher risks of cardiometabolic multimorbidity in patients with hypertension.
- A higher frequency of night shifts is associated with increased risk of cardiometabolic multimorbidity that is even more pronounced for >10/month in combination with a morning chronotype or <7 hours or >8 hours sleep duration.

What Are the Clinical Implications?

- Our findings suggest that intervention in work schedules might be one way to reduce susceptibility to cardiometabolic multimorbidity among patients with hypertension.

Nonstandard Abbreviations and Acronyms

CMD	cardiometabolic disease
CMM	cardiometabolic multimorbidity

poor prognosis of CMM, risk factors for progression to CMM among patients with hypertension are cause for more concern than they have received. Previous studies have examined the association between many lifestyle behaviors and the risk of CMM in patients with CMDs, such as alcohol consumption, level of physical activity, and smoking.[8,9] However, no previous study has investigated the role of shift work, especially night shift work, in the progression from hypertension to CMM.

The effects of shift work on several single CMDs have already received much attention. Shift work is defined as work during nonstandard working hours (anywhere from 18:00 to 07:00), including afternoon, night, and rotating through these shifts.[10,11] Globally, shift work is highly prevalent, involving about 20% each of the European and the American workforces.[12] Sleeping patterns, hormone secretion, core body temperature and other biological activities are all influenced by the circadian disruption during shift work, which may lead to metabolic disorders and which may be a potential risk factor for cardiovascular diseases.[13,14] Growing evidence indicates that shift work is related to increased risk of cardiovascular disease,[15,16] hypertension,[17] type 2 diabetes,[18] and other adverse health outcomes[19,20] in otherwise healthy individuals. Research has shown that there is a positive association between night shift work and the risk of many common CMDs. However, we cannot assume that this association applies to the risk of CMM in patients with hypertension because research has also shown that one risk factor may exhibit distinct effects in different processes in the course of CMDs, such as from healthy state to the single CMD state, or the single CMD state to CMM.[8,9]

To our knowledge, no previous study has evaluated the role of shift work in the progression to CMM among patients with hypertension. Hence, we investigate the association between current shift work and risk of CMM in patients with hypertension. Further, we examine the relationship between lifetime duration and frequency of night shift work and CMM risks as well. In addition, we conducted a cross-classification analysis in which we explored the association between cross-classified duration and frequency of night shift work, chronotype, and sleep duration and CMM risks.

METHODS

The data and methods that support the findings of this study are available from the corresponding authors upon reasonable request.

Study Population

UK Biobank is a prospective study that recruited >500 000 participants from the United Kingdom. All people who were aged 40 to 69 years and living within a 25-mile radius of a UK Biobank assessment center were invited to participate between 2006 and 2010. Participants were recruited from >9.2 million mailed invitations, and baseline data (questionnaires, interviews, and physical measurements) were collected at 21 assessment centers across the United Kingdom. At the baseline visit, participants completed questionnaires on lifestyle, medical history, and work hours, and medical conditions, health status, and medications were queried by trained health professionals. The UK Biobank has full ethical approval from the National Health Service National Research Ethics Service (16/NW/0274), and all participants provided written informed consent.

Of the 502 414 UK Biobank participants, 286 291 participants had some form of paid employment or were self-employed at baseline. Of these, we included 52 230 participants with hypertension and without coronary heart disease, stroke, or diabetes. Participants who had missing data (n=15 291; n=10 175 because of missing data on physical activity) were excluded, leaving 36 939 participants for the main analysis. Among these, only 17 639 participants had in-depth lifetime employment information available for analysis about shift work frequency and duration (Figure S1).

Shift Work Assessment

Employed participants were invited to complete an employment questionnaire, in which they reported whether their current work involved shift work (a schedule falling

outside of 09:00 to 17:00) with 4 options: never/rarely, sometimes, usually, or always. This could involve working afternoons, nights, or rotating through these kinds of shifts. All participants except those that "never" performed shift work were further asked whether their job involved night shifts, which were defined as work schedules that involve working through normal, diurnal sleeping hours (working through the hours from 00:00 to 06:00). Participants could respond never/rarely, sometimes, usually, or always.

Participants were then divided into 4 groups based on their answers to the employment questionnaires: day workers, shift workers with never/rarely night shifts, shift workers with some night shifts, and shift workers with usually/always night shifts. Some of these participants also completed a lifetime employment survey and reported each job they ever worked and the duration (the number of years spent working night shifts) and frequency (the average number of night shifts per month) of night shifts for each job. From this lifetime employment information, participants were categorized as day workers, 1 to 10 night shifts per month, or >10 night shifts per month in the analysis of the frequency of night shifts and categorized as day workers, 1 to 10 years of night shift work, or >10 years of night shift work in analysis of the duration of night shifts.

Ascertainment of CMM

In this study, CMM was defined as the presence of ≥1 of the following CMDs based on hypertension: coronary heart disease, stroke, or diabetes. Participants were regarded as cases of CMDs if they had a self-reported diagnosis, surgical history, CMD medication history, electronic health record, or verbal interview that was consistent with the diagnosis of CMD. For CMM, the date of onset was the earliest date of the second CMD record during the follow-up period ascertained via any of the data sources. The detailed diagnostic criteria are shown in Table S1.

Covariates

For our multivariate analysis we included information on sociodemographic and lifestyle behaviors, including age, sex, race, area-based Townsend deprivation index, education, alcohol consumption, smoking status, body mass index (BMI), chronotype, sleep duration, physical activity, drug use (antihypertension drugs, lipid-lowering drugs, and aspirin). The area-based Townsend deprivation index was used as a composite measure of deprivation based on unemployment, non-car ownership, nonhome ownership, and household overcrowding, where negative values represent less deprivation. Physical activity was evaluated at recruitment based on the International Physical Activity Questionnaire on the frequency and duration of different-intensity activities. Participants were separated into 2 groups based on whether they met the 2017 UK physical activity guidelines of 150 minutes of walking or moderate activity per week or 75 minutes of vigorous activity. BMI was calculated by dividing the weight (kg) by height squared (m^2). Additionally, participants were regarded as having a healthy diet pattern if they met the standard derived from the American Heart Association Guidelines, which was defined as follows: at least 2 servings of healthy food items including ≥2 servings of fish per week, ≥4.5 servings of fruit and vegetables per week, ≤2 servings of processed meat per week, and ≤5 servings of red meat per week.

Statistical Analysis

The baseline characteristics of participants were expressed as mean (SD) or number (percentage) and compared among different shift work groups using 1-way ANOVA and Chi-square tests for continuous and categorical variables, respectively. Because death may prevent the observation of potential incidence of CMM, we used a Fine and Gray competing risk model to calculate the association between shift work and risks of CMM. Using the group of day workers as a reference, we analyzed the hazard ratio (HR) and 95% CI on shift work status (shift but never/rarely night shifts, some night shifts, and usually/always night shifts) using multivariable competing risk models. For participants reporting lifetime employment, we analyzed the relationship between CMM risks and cumulative night shift work duration (day workers, 1–10 years, and >10 years) and average monthly frequency of night shifts (day workers, 1–10 nights/month, and >10 nights/month), respectively. In addition, considering the obvious effects of night shift work on sleep deprivation and chronotype, we also conducted a cross-classification analysis using the combination of frequency (day workers, 1–10 years, and >10 years) and duration of night shifts (day workers, 1–10 nights/month, and >10 nights/month), chronotype (morning type and evening type), and sleep duration (<7 hours and >8 hours and 7–8 hours) as exposure metrics.

In total we fitted 3 multivariate-adjusted models in our analysis for current shift work and in analysis for duration and frequency of night shift work. In model 1, we initially adjusted for age and sex. Model 2 additionally adjusted for race or ethnicity, area-based Townsend deprivation index, education, alcohol consumption, smoking status, BMI, physical activity, antihypertensive medication use, lipid-lowering medication use, and aspirin use. Finally, model 3 also included chronotype and sleep duration in addition to the covariates in model 2. Model 2 were fitted in the cross-classification analysis.

To examine whether the association between current shift work and CMM risks was persistent in different subgroups, we conducted a stratification analysis with the following factors: sex, sleep duration (<7 hours, >8 hours and 7–8 hours), BMI (≥25.0 kg/m^2 and <25.0 kg/m^2), smoking status (current smokers and never/previous smokers), alcohol consumption (<3/week and ≥3/week), physical activity (physically active and physically inactive), and chronotype (morning type and evening type). In addition, we conducted 4 sensitivity analyses. First, we recalculated the association between shift work and CMM risks excluding new cases of CMM within 2 years of follow-up to decrease the impact of confounding factors before recruitment. Second, we recalculated the analysis excluding the participants who died within the first 2 years of follow-up to minimize reverse causality. Third, to decrease the confounding effects created by participants who already had metabolic syndrome at baseline, we conducted the analysis excluding participants with metabolic syndrome at baseline. Fourth, we recalculated the analyses excluding the use of verbal interview in the diagnosis of CMDs to minimize the impacts of misreporting. All statistical analysis was performed using R software (version 4.1.0). We consider 2-tailed $P<0.05$ to indicate a statistically significant test result.

RESULTS

Characteristics of the Study Population

The baseline characteristics of 36 939 enrolled patients who were divided into 4 groups according to their work status are expressed in Table 1. Among shift workers,

Table 1. Baseline Characteristics of 36 939 Patients With Hypertension Categorized by Current Night Shift Work

Baseline characteristics*	Current work schedule			
	Day workers	Shift but never/rarely night shifts	Some night shifts	Usually/always night shifts
No.	30 800	3065	1762	1312
Age, y	55.69 (6.75)	55.11 (6.87)	54.05 (6.69)	54.21 (6.54)
Men (%)	16 172 (52.5)	1617 (52.8)	1215 (69.0)	874 (66.6)
Race (%)				
White	29 351 (95.3)	2789 (91.0)	1564 (88.8)	1154 (88.0)
Black	571 (1.9)	107 (3.5)	104 (5.9)	86 (6.6)
Asian	519 (1.7)	96 (3.1)	46 (2.6)	40 (3.0)
Other‖	359 (1.2)	73 (2.4)	48 (2.7)	32 (2.4)
BMI, kg/m^2	28.88 (4.97)	29.63 (5.27)	29.98 (4.91)	30.03 (5.13)
Townsend index	−1.52 (2.93)	−0.53 (3.23)	−0.69 (3.27)	−0.34 (3.29)
Current smokers (%)	2675 (8.7)	387 (12.6)	227 (12.9)	182 (13.9)
Heavy alcohol consumers† (%)	15 209 (49.4)	1283 (41.9)	744 (42.2)	489 (37.3)
Blood pressure medication (%)	17 271 (56.1)	1712 (55.9)	963 (54.7)	762 (58.1)
Cholesterol lowering medication (%)	6111 (19.8)	605 (19.7)	341 (19.4)	259 (19.7)
Aspirin (%)	4147 (13.5)	430 (14.0)	214 (12.1)	170 (13.0)
Morning chronotype (%)	19 677 (63.9)	1927 (62.9)	1101 (62.5)	681 (51.9)
Sleep duration (%)				
<7 h	8224 (26.7)	978 (31.9)	626 (35.5)	539 (41.1)
7–8 h	21 125 (68.6)	1946 (63.5)	1046 (59.4)	693 (52.8)
>8 h	1451 (4.7)	141 (4.6)	90 (5.1)	80 (6.1)
Physically active‡ (%)	23 683 (76.9)	2561 (83.6)	1503 (85.3)	1126 (85.8)
Healthy diet§ (%)	16 880 (54.8)	1650 (53.8)	888 (50.4)	661 (50.4)
College or higher/professional education (%)	22 618 (73.4)	2118 (69.1)	1282 (72.8)	886 (67.5)

BMI indicates body mass index.

*Values are expressed as mean (SD) or number (percentage).

†Heavy alcohol consumers defined as consuming alcohol ≥3 times per week.

‡Physically active defined as meeting the 2017 UK Physical activity guidelines of 150 minutes of walking or moderate activity per week or 75 minutes of vigorous activity.

§Healthy diet defined as meeting the standard derived from American Heart Association Guidelines: at least 2 healthy food items including ≥4.5 servings fruit and vegetable intake per week, ≥2 servings fish intake per week, ≤2 times processed meat per week, and ≤5 times red meat per week.

‖"Others" mainly refers to people with mixed ethnic background, including white and black caribbean, white and black African, white and Asian or any other mixed background

Table 2. Association Between Current Night Shift Work and CMM Risks Among Patients With Hypertension in the UK Biobank

	Current work schedule						
	Day workers	Shift but rarely/ever night shifts		Some night shifts		Usually/always night shifts	
Total cases	4792	548		324		275	
Total sample size	30 800	3065		1762		1312	
	HR	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Model 1*	1 (ref)	1.20 (1.10–1.31)	<0.001	1.20 (1.07–1.35)	0.001	1.36 (1.21–1.54)	<0.001
Model 2†	1 (ref)	1.08 (0.99–1.18)	0.084	1.08 (0.97–1.21)	0.180	1.17 (1.03–1.32)	0.017
Model 3‡	1 (ref)	1.08 (0.99–1.18)	0.093	1.08 (0.96–1.20)	0.210	1.16 (1.02–1.31)	0.025

CMM indicates cardiometabolic multimorbidity; and HR, hazard ratio.
*Adjusted for age and sex.
†Adjusted for variables in model 1 plus race or ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, antihypertensive medication use, lipid-lowering medication use, and aspirin use.
‡Adjusted for variables in model 2 plus sleep duration and chronotype.

around half (*n*=3074) worked night shifts. Compared with day workers, shift workers were younger, tended to be men, and tended to be more deprived. In addition, they were more likely to smoke, sleep less, have a lower education level, and have a higher BMI.

Current Night Shift Work and CMM

During a median of 11.6 years of follow-up, a total of 5935 participants developed CMM. We first examined the association between current shift work and CMM risks in patients with hypertension. In model 3, usually/always night shifts workers were associated with a 16% higher risk (HR, 1.16 [95% CI, 1.02–1.31]) of CMM compared with day workers with adjustments for age, sex, race or ethnicity, BMI, lifestyle behavior factors, medication use, sleep duration, and chronotype (Table 2).

Lifetime Duration of Night Shift Work and CMM Risk

We further investigated the association between lifetime night shift duration and CMM risk in 17 639 patients with hypertension. Model 1 suggested that lifetime night shift work duration of ≤10 years was associated with higher CMM risks (Table 3), but this association became insignificant after adjustments in models 2 and 3.

Average Lifetime Frequency of Night Shifts and CMM Risk

Similarly, we found that higher night shift frequency was associated with higher CMM risks after adjustments (Table 4). In model 3, higher frequency of night shift work (>10 night shifts per month) was associated with a 19% higher risk (HR, 1.19 [95% CI, 1.06–1.34]) of CMM compared with day workers with adjustments for age, sex, race or ethnicity, BMI, lifestyle behavior factors, medication use, sleep duration, and chronotype.

Shift Work and CMM Risk With Cross-Classification Analysis

When we cross-classified the chronotype, sleep duration, frequency, and duration of night shift work

Table 3. Association Between Lifetime Duration of Night Shift Work and CMM Risk Among Patients With Hypertension

	Lifetime duration of night shift work					*P*-trend
	None	1–10 y		>10 y		
Total cases	2411	305		95		
Total sample size	15 597	1561		481		
	HR	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
Model 1*	1 (ref)	1.16 (1.03–1.31)	0.018	1.17 (0.95–1.44)	0.140	0.066
Model 2†	1 (ref)	1.12 (0.99–1.26)	0.076	1.10 (0.89–1.35)	0.390	0.260
Model 3‡	1 (ref)	1.11 (0.98–1.25)	0.099	1.09 (0.88–1.34)	0.420	0.290

CMM indicates cardiometabolic multimorbidity; and HR, hazard ratio.
*Adjusted for age and sex.
†Adjusted for variables in model 1 plus race or ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, antihypertensive medication use, lipid-lowering medication use, and aspirin use.
‡Adjusted for variables in model 2 plus sleep duration and chronotype.

Table 4. Association of Average Lifetime Frequency of Night Shifts and CMM Risk Among Patients With Hypertension

	Average lifetime night shift frequency					*P*-trend
	None	1–10/mo		>10/mo		
Total cases	1970	510		331		
Total sample size	13327	2767		1545		
	HR	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
Model 1*	1 (ref)	1.21 (1.10–1.34)	<0.001	1.37 (1.21–1.54)	<0.001	<0.001
Model 2†	1 (ref)	1.14 (1.03–1.26)	0.010	1.20 (1.06–1.35)	0.003	<0.001
Model 3‡	1 (ref)	1.14 (1.03–1.25)	0.013	1.19 (1.06–1.34)	0.005	0.001

CMM indicates cardiometabolic multimorbidity; and HR, hazard ratio.

*Adjusted for age and sex.

†Adjusted for variables in model 1 plus race or ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, antihypertensive medication use, lipid-lowering medication use, and aspirin use.

‡Adjusted for variables in model 2 plus sleep duration and chronotype.

variables, we found that the risk of CMM was greater among participants with hypertension for >10 night shifts per month in combination with morning chronotype (HR, 1.26 [95% CI, 1.02–1.56]), for >10 night shifts per month in combination with <7 hours or >8 hours sleep duration (HR, 1.43 [95% CI, 1.19–1.72]), for ≤10 night shifts per month in combination with morning chronotype (HR, 1.22 [95% CI, 1.03–1.46]), for ≤10 night shifts per month in combination with <7 hours or >8 hours sleep duration (HR, 1.31 [95% CI, 1.12–1.53]), and for ≤10 years night shift work with <7 hours or >8 hours sleep duration (HR, 1.24 [95% CI, 1.01–1.51]) (Table 5).

Stratified and Sensitivity Analysis

In stratified analysis, compared with day workers, for those with a BMI <25.0 kg/m^2, shift but rarely/ever night shifts and usually/always nights shift work showed more increased CMM risk (*P*-interaction=0.017). In addition, the association between current night shifts and CMM showed non-significant differences when stratified by sex, sleep duration, chronotype, alcohol consumption, smoking status, and physical activity (Figure). Besides, all 4 sensitivity analyses were broadly consistent with the results in the main analysis, indicating the robustness of our study (Tables S2 through S5).

DISCUSSION

In this large-scale cohort with a median follow-up of 11.6 years, we found the following: first, patients with hypertension who were shift workers were at higher risk for the development of CMM than day workers, and usually/always night shift workers had the highest risk of CMM; second, higher average night shift frequency per month was associated with higher risk of CMM; third, higher average night shift frequency per month with morning chronotype or sleep duration <7 hours or >8 hours showed stronger association with the development of CMM.

To our knowledge, our investigation is the first study to report the association of night shift work with the transition from hypertension to CMM. However, we do indeed build upon previous literature. In a prospective cohort study of 238 661 participants from the UK Biobank, Ho et al reported that night shift workers had an 11% and 25% increased risk of cardiovascular disease events and mortality, respectively than day workers in the general population.[21] In addition one dose–response meta-analysis with 5 cohort studies demonstrated that an increase in shift work of 5 years was associated with a 5% increase in the risk of cardiovascular diseases and 4% increase in the cardiovascular diseases mortality risk.[22] Our analyses extend these findings and focuses on the progression from a single CMD to CMM. In line with previous studies, we find that shift work increased the risk of progression from hypertension to CMM, and this elevated risk especially related to current usually/always night shift work. Although permanent night shift workers were more likely to be late chronotypes, which tended to make them tolerate shift work better, Folkard found that only a small minority (<3%) of permanent night shift workers appear to adjust their endogenous circadian timing adequately to night work, as assessed by the circadian rhythmicity of melatonin.[23]

Several individuals with hypertension from our sample were still shift-working at the time of follow-up. Among workers with hypertension, around 17% were shift workers in our study. However, clinical guidelines did not refer to CMM prevention among shift workers with hypertension. Our findings suggest that intervention in work schedules might reduce susceptibility to CMM among patients with hypertension. The potential mechanism underlying the link between shift work and CMM is unclear, but it may be because shift work increases the risk of dyslipidemia and elevated glucose,[24]

Table 5. Association Between Shift Work and CMM Risk by Cross-Classification Analysis Among Patients With Hypertension

Night work exposure*	n	HR	95% CI	*P* value
Frequency of night shifts and circadian preference				
Day workers and intermediate (ref)	8660			
≤10/mo, morning	740	1.22	1.03–1.46	0.024
≤10/mo, evening	266	1.42	0.98–1.85	0.211
>10/mo, morning	420	1.26	1.02–1.56	0.030
>10/mo, evening	146	1.03	0.70–1.51	0.900
Frequency of night shifts and sleep duration				
Day workers, 7 to 8 h (ref)	9460			
≤10/mo, 7 to 8 h	1873	1.13	0.99–1.28	0.055
≤10/mo, <7 h or >8 h	894	1.31	1.12–1.53	<0.001
>10/mo, 7 to 8 h	992	1.16	0.99–1.35	0.060
>10/mo, <7 h or >8 h	553	1.43	1.19–1.72	<0.001
Duration of night shifts and circadian preference				
Day workers and intermediate (ref)	10069			
≤10 y, morning	401	1.19	0.95–1.48	0.140
≤10 y, evening	153	1.22	0.94–1.87	0.110
>10 y, morning	118	0.93	0.58–1.39	0.640
>10 y, evening	39	1.22	0.66–2.50	0.460
Duration of night shifts and sleep duration				
Day workers, 7 to 8 h (ref)	10975			
≤10 y, 7 to 8 h	1030	1.15	0.99–1.34	0.070
≤10 y, <7 h or >8 h	531	1.24	1.01–1.51	0.037
>10 y, 7 to 8 h	320	1.27	0.99–1.63	0.059
>10 y, <7 h or >8 h	161	0.95	0.65–1.39	0.790
Duration and frequency of night shifts				
Day workers (ref)	13327			
≤10/mo and ≤10 y	996	1.13	0.97–1.32	0.120
≤10/mo and >10 y	341	1.14	0.89–1.47	0.290
>10/mo and ≤10 y	565	1.18	0.98–1.43	0.083
>10/mo and >10 y	140	1.08	0.74–1.57	0.700

CMM indicates cardiometabolic multimorbidity; and HR, hazard ratio.

*Adjusted for age, sex, race or ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, antihypertensive medication use, lipid-lowering medication use, and aspirin use.

circadian disruption, and systemic inflammation,[25] and reduced melatonin production,[26,27] which can be pathways to the development of both CMM and single CMD.

In addition, our findings also add to the literature by highlighting the role of night shift frequency based on lifetime employment reports. A prospective cohort of nurses found that individuals who had >5 to 10 or >10 night shifts per month were significantly more likely to be hypertensive,[28] and another study found that the monthly frequency of night shifts worked is key for type 2 diabetes risk.[29] Consistent with these observations, we find that participants with hypertension who on average worked >10 night shifts per month had a significant, 19% higher likelihood of CMM compared with participants who never worked night shifts. Thus, reducing night shift work frequency might be useful in improving metabolic health during working lives of patients with hypertension.

In addition to the frequency of night shifts, previous studies have shown that the duration of night shift work can also affect cardiovascular health.[30] In the Nurses' Health Study with 22 to 24 years of follow-up, compared with non-shift work, women with <5, 5 to 9, and ≥10 years of shift work history had coronary heart disease risks of 1.02, 1.12, and 1.18, respectively.[16] We did not find a linear association between duration of night shift work and the prevalence of CMM in participants with hypertension. Differences in study design, disease spectra and number, population characteristics (differences in genes, environmental, and behavioral factors), and the healthy worker effect, where shift workers stop working night shifts once their health declines, may partly explain this insignificant association.[31]

Chronotype and sleep duration have been pointed out as factors that can potentially mediate the tolerance of shift work.[32] Interestingly, however, we observed an increased risk of CMM when night work indicators were jointly examined, particularly for >10 night shifts per month in combination with morning chronotype, and for >10 night shifts per month in combination with <7 hours or >8 hours sleep duration. The cumulative number of night shifts, the average length of night shifts, short shift intervals, and consecutive night shifts might also be related to health. There were insufficient participants who worked night shifts to provide this information in the UK Biobank; however, future studies could explore whether these exposure metrics were differentially associated with CMM.

In stratified analysis, we find that the association between shift work and CMM was markedly stronger in individuals with a BMI <25.0 kg/m^2, especially for usually/always night shift work. We speculate that individuals with lower BMI are more susceptible to changes in circadian rhythms. One reason for the effects of shift work comes from circadian misalignment. Morning chronotypes find it particularly difficult to adjust to working night shifts and display higher levels of circadian misalignment than evening chronotypes.[33] In addition, Nicolaides et al suggest that women are more susceptible to circadian misalignment,[34] and we examined potential interactions between chronotype, sex, and shift work for CMM, but observed no interaction effect. Moreover, the association between current night shifts and CMM did not appear to be modified by sleep duration, alcohol consumption, smoking status, or physical activity.

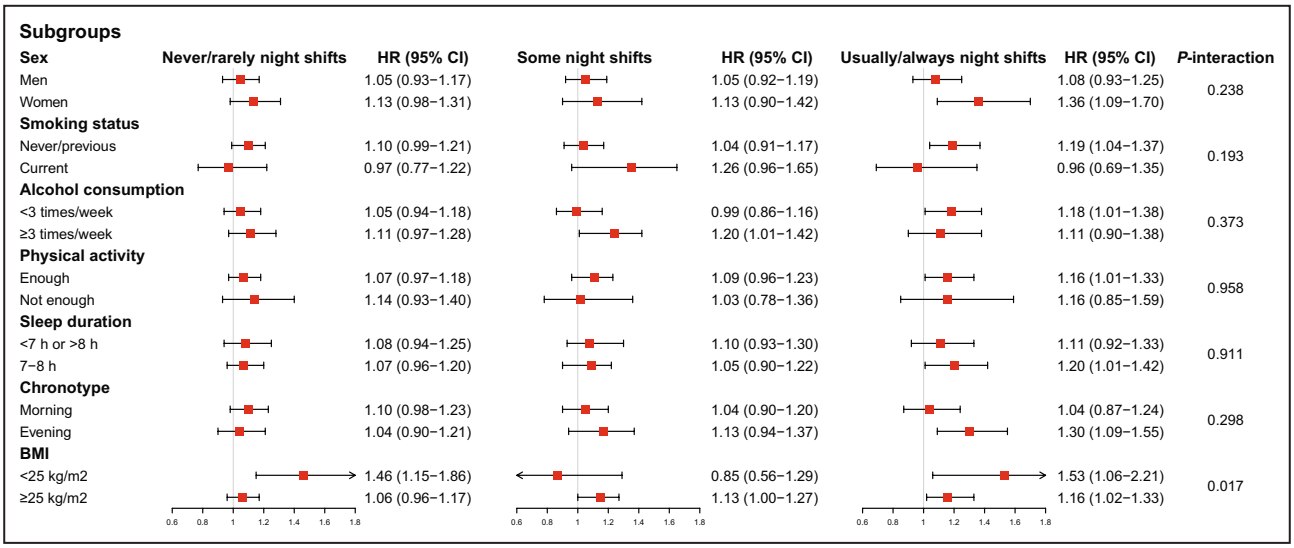

Figure. Current night shift work and cardiometabolic multimorbidity risk among patients with hypertension in the UK Biobank stratified by potential risk factors.

Associations of shift work and risk of cardiometabolic multimorbidity were stratified by body mass index, sex, sleep duration, chronotype, alcohol consumption, smoking status, and physical activity. The model was adjusted for age, sex, race or ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, sleep duration, chronotype, antihypertensive medication use, lipid-lowering medication use, and aspirin use. BMI indicates body mass index; and HR, hazard ratio.

Strengths and Limitations

Our study has several strengths. First, this is the largest prospective cohort study on shift work and the progression from hypertension to CMM ever conducted. Second, >70 000 individuals provided a detailed employment history, allowing us to categorize duration and frequency of shifts, thus overcoming limitations of many previous studies. Third, participants in the UK Biobank were selected entirely independent of employment status, and therefore the participants represented an unbiased sample of the whole UK workforce. This minimized the potential selection bias introduced when studying a single occupation for example. However, the present study does still have its limitations.

To begin, considering the observational nature of our investigation, we cannot infer direct causality for any of our findings. Second, the assessment of shift work and the diagnosis of CMDs included information from self-reports and verbal interviews, which can suffer from the problem of misreporting. However, a recent study has compared working time information based on questionnaires and has highly validated self-reported assessment of shift work with night work and permanent night shifts, thus supporting our exposure assessment method.[35] We also conducted a sensitivity analysis that excluded verbal interviews in the diagnosis of CMD, and the results showed no significant differences from our main analysis. Third, current and lifetime employment information were measured in the baseline assessment and could have changed over time. Nonetheless, this is likely to bias our results toward the null hypothesis and thus underestimated the effect. Furthermore, despite our large sample size, our analysis is restricted to adults aged 40 to 69 years; the UK Biobank provides no data on younger people and is limited to a predominately White population. Therefore, results may require validation for other age groups and races or ethnicities. Although we carefully adjusted for several covariates, residual confounding is still possible. Finally, a limitation of the UK Biobank data is that participation rates were low at ≈5%, which may have introduced selection bias.

CONCLUSIONS

In this study, we found an increased risk of progression from hypertension to CMM in shift workers who work usually/always night shifts as compared with day workers. Furthermore, night shift work frequency appears to be relevant for CMM risks in patients with hypertension. Hence, modification of shift schedules might be a novel step in attenuating the further rise of CMM prevalence among patients with hypertension.

ARTICLE INFORMATION

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Affiliations

Xiangya International Medical Center, Xiangya Hospital, Central South University, Changsha, Hunan, China (L.Y., D.L.); Department of Cardiovascular Medicine, The Third Xiangya Hospital, Central South University, Changsha, Hunan, China (Y.L.); Department of Geriatric Medicine, Center of Coronary Circulation (L.Y., Y.L., L.H., J.Y., D.L., X.C., Y.B.); National Clinical Research

Center for Geriatric Disorders (L.Y., L.H., J.Y., D.L., X.C., Y.B.); and Department of General and Vascular Surgery (S.L.), Xiangya Hospital, Central South University, Changsha, Hunan, China; and Department of Cardiovascular Medicine, Changsha County Second People's Hospital, Changsha, Hunan, China (T.L.).

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Specific diagnostic criteria for coronary heart disease, hypertension, stroke and diabetes

Disease	Coronary heart disease	Hypertension	Diabetes	Stroke
Self-report	angina and myocardial infarction/heart attack self-report	hypertension self-report	diabetes self-report	stroke self-report
Medication history	/	blood pressure medication	insulin	/
Surgery history	coronary angioplasty, coronary artery bypass grafts and triple heart bypass	/	/	/
ICD-9	410-414	401-405	250, 3572, 3620	3361, 36231, 36232, 430, 431, 4329, 43301, 43311, 43321, 43331, 43381, 43391, 434, 436
ICD-10	I20-I25, Z95.1, Z95.5	I10-I13, I15, O10	E10-E14, G59.0, G63.2, H28.0, H36.0, M14.2, N08.3	I60, I61, I62.9, I63, I64, I67.8, I69.0, I69.3, G95.1, H34.1, H34.2, S06.6
OPCS-4	K40-K46, K49, K50, K75	/	/	A05.2-A05.4, L35.1, L35.3, L34.3

Abbreviations: ICD-9, International Classification of Diseases version 9; ICD-10, International Classification of Diseases version 10; OPCS-4, Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4.

Table S2. The association between current night shift work and CMM risk excluding new cases of CMM within 2 years of follow-up

	Current work schedule						
	Day workers	Shift but rarely/ever night shifts		Some night shifts		usually/always night shifts	
Total cases	4042	469		271		229	
Total sample size	29944	2975		1702		1265	
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Model 1*	1.00(ref)	1.20 (1.06-1.35)	<0.001	1.20 (1.06-1.35)	0.004	1.37 (1.20-1.57)	<0.001
Model 2†	1.00(ref)	1.10 (0.99-1.21)	0.060	1.07 (0.95-1.21)	0.270	1.17 (1.02-1.34)	0.028
Model 3‡	1.00(ref)	1.10 (0.99-1.21)	0.066	1.07 (0.94-1.21)	0.310	1.15 (1.02-1.31)	0.038

Abbreviations: CI, confidence interval; CMM, cardiometabolic multimorbidity; HR, hazard ratio; ref, reference.

* adjusted for age and sex

† adjusted for variables in model 1 plus ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, antihypertensive medication use, lipid-lowering medication use, and aspirin use

‡ adjusted for variables in model 2 plus sleep duration and chronotype

Table S3. The association between current night shift work and CMM risk excluding participants who died within the first 2 years of follow-up

	Current work schedule						
	Day workers	Shift but rarely/ever night shifts		Some night shifts		usually/always night shifts	
Total cases	4764	543		322		270	
Total sample size	30696	3051		1755		1309	
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Model 1*	1.00(ref)	1.19 (1.09-1.31)	<0.001	1.20 (1.07-1.35)	0.002	1.37 (1.21-1.54)	<0.001
Model 2†	1.00(ref)	1.08 (0.99-1.18)	0.094	1.08 (0.96-1.21)	0.190	1.17 (1.03-1.32)	0.017
Model 3‡	1.00(ref)	1.08 (0.99-1.18)	0.100	1.07 (0.96-1.20)	0.220	1.16 (1.02-1.31)	0.024

Abbreviations: CI, confidence interval; CMM, cardiometabolic multimorbidity; HR, hazard ratio; ref, reference.

* adjusted for age and sex

† adjusted for variables in model 1 plus ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, anti-hypertensive medication and lipid-lowering medication, and aspirin

‡ adjusted for variables in model 2 plus sleep duration and chronotype

Table S4. The association between current night shift work and CMM risk excluding participants with metabolic syndrome at baseline

	Current work schedule						
	Day workers	Shift but rarely/ever night shifts		Some night shifts		usually/always night shifts	
Total cases	2658	273		151		147	
Total sample size	20724	1903		1087		804	
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Model 1*	1.00(ref)	1.17 (1.03-1.32)	0.150	1.09 (0.92-1.28)	0.320	1.45 (1.23-1.71)	<0.001
Model 2†	1.00(ref)	1.04 (0.91-1.18)	0.560	0.98 (0.83-1.16)	0.820	1.24 (1.05-1.47)	0.012
Model 3‡	1.00(ref)	1.03 (0.91-1.18)	0.600	10.98 (0.83-1.15)	0.770	1.23 (1.04-1.45)	0.017

Abbreviations: CI, confidence interval; CMM, cardiometabolic multimorbidity; HR, hazard ratio; ref, reference.

* adjusted for age and sex

† adjusted for variables in model 1 plus ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, anti-hypertensive medication and lipid-lowering medication, and aspirin

‡ adjusted for variables in model 2 plus sleep duration and chronotype

Table S5. The association between current night shift work and CMM risk excluding the use of verbal interview in the diagnosis of cardiometabolic diseases

	Current work schedule						
	Day workers	Shift but rarely/ever night shifts		Some night shifts		usually/always night shifts	
Total cases	4785	546		324		270	
Total sample size	30723	3060		1758		1311	
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Model 1*	1.00(ref)	1.19 (1.09-1.30)	<0.001	1.20 (1.07-1.35)	0.001	1.36 (1.20-1.54)	<0.001
Model 2†	1.00(ref)	1.08 (0.99-1.18)	0.098	1.08 (0.97-1.21)	0.170	1.16 (1.02-1.32)	0.020
Model 3‡	1.00(ref)	1.08 (0.99-1.18)	0.110	1.08 (0.96-1.21)	0.200	1.15 (1.01-1.31)	0.029

Abbreviations: CI, confidence interval; CMM, cardiometabolic multimorbidity; HR, hazard ratio; ref, reference.

* adjusted for age and sex

† adjusted for variables in model 1 plus ethnicity, smoking status, alcohol consumption, Townsend Deprivation Index, physical activity, body mass index, education, antihypertensive medication use, lipid-lowering medication use, and aspirin use

‡ adjusted for variables in model 2 plus sleep duration and chronotype

Figure S1. Flow chart of the study population