Night Shift Work is Associated with Elevated Risk of Knee Osteoarthritis and Total Knee Arthroplasty

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INTRODUCTION: Accumulating evidence has indicated the importance of circadian rhythms in maintaining homeostasis of the articular cartilage and other joint tissues. In rodent models, genetic or environmental disruption of the circadian clock can lead to osteoarthritis (OA)-like cartilage degeneration.[1-2] Conversely, changes in clock gene expression have been observed in OA cartilage from both mice and humans.[3-4] However, few studies have investigated the relationship between circadian clock disruption and OA risk in human populations. Shift work, particular night shift work, is a key example of such a disruption in the real-world. Using the UK Biobank, a 500,000-person cohort, we hypothesized that shift work would be associated with higher rates of knee and hip OA diagnoses, as well as higher rates of total knee arthroplasty (TKA) and total hip arthroplasty (THA).

METHODS: At the UK Biobank baseline assessment visit, participants completed surveys including questions on demographics and shift work frequency and had physical measurements taken, including weight and height to calculate body mass index (BMI). Participants were then followed through linkages with hospital records for the full cohort, and primary care records for half the cohort. Our study population was derived from the participants employed and reporting shift work status at baseline. Associations with TKA and THA were evaluated in the full cohort with hospital records, with cases defined as the presence of corresponding procedure codes accompanied by an OA diagnosis before or at the time of the procedure. Associations with hip and knee OA were evaluated in participants with linked primary care records that did not report prevalent OA at baseline. An incident OA case was defined as the presence of ≥2 hip/knee OA diagnosis codes within six months. Cox regression was used to estimate associations between shift work and OA outcomes adjusting for age, sex, education, race, Townsend Deprivation Index, and frequency of manual work. Associations with and without adjustment for body mass index were estimated, as circadian clock disruption may influence OA through effects on obesity.

RESULTS: Among the 286,370 participants reporting shift work frequency, 24,215 (8%) reported doing shift work only during the day, and 25,357 (9%) reported doing night shift work. Shift workers were more likely to be male, non-White, and have less than a college education. Shift workers also reported more frequent heavy manual work and were more likely to have a BMI categorized as obese (BMI≥30 kg/m^2). Compared to workers that did not work shifts, day shift workers had 8% higher risk of knee OA (P=0.141) and 14% higher risk of TKA (95%CI=5%-23%, P=0.001) after adjusting for age, sex, race, education, Townsend Deprivation Index, and frequency of manual work (Table 1). In the same analyses, night shift workers had 25% higher risk of knee OA (95%CI=13%-39%, P<0.001) and 30% higher risk of TKA (95%CI=21%-41%, P<0.001) compared to non-shift workers. After additionally adjusting for BMI, all associations were attenuated, but night shift work remained significantly associated with both knee OA and TKA (Table 1). Evaluation of day shift and night shift frequency (reported as work that "Sometimes", "Usually", or "Always" involves shift work) did not indicate a trend between increasing frequency of shift work and higher risk of knee OA or TKA. Day shift and night shift work were not associated with hip OA or THA, regardless of adjustment for BMI (Table 2).

DISCUSSION: Disruption of the circadian clock may be a novel risk factor for knee OA that influences cartilage degeneration both through effects on obesity and through obesity-independent pathways. Increasing shift work frequency may not heighten risk because occasional shift work may be as disruptive to the circadian clock as consistent shift work. The lack of associations with hip OA outcomes may reflect both the weaker contribution of obesity to hip OA etiology and the differing mechanisms through which hip OA develops (i.e., hip dysplasia and impingement). Further studies are needed to determine the interaction of shift work with other OA risk factors such as aging, injury, or genetics.

SIGNIFICANCE/CLINICAL RELEVANCE: As circadian clock disruptions can be reduced through lifestyle changes and chronotherapy, these findings point to new potential ways to prevent knee OA development and progression.

REFERENCES: 1. Bekki et al. *Osteoarthr Cartil.* 2020;28(7):966-976. **2.** Kc et al. *J Cell Physiol*. 2015;230(9):2174-2183. **3.** Fisch et al. *Osteoarthr Cartil.* 2018;26(11):1531-1538. **4.** Gossan et al. *Arthritis Rheum*. 2013; 65(9):2334-2345.

Table 1. Associations of shift work with knee OA and TKA*

	Without *adjustment for BMI*				With *adjustment for BMI*			
	Knee OA		**TKA**		**Knee OA**		**TKA**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Type of Shift Work								
None	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Only Day Shifts	1.08 (0.97-1.21)	0.141	1.14 (1.05-1.23)	0.001	1.04 (0.93-1.16)	0.502	1.07 (0.99-1.16)	0.075
Night Shifts	1.25 (1.13-1.39)	<0.001	1.30 (1.21-1.41)	<0.001	1.16 (1.05-1.29)	0.004	1.18 (1.10-1.28)	<0.001

All models adjusted for age, sex, education, race, Townsend Deprivation Index, and frequency of manual/physical labor. HR=Hazard Ratio

Table 2. Associations of shift work with hip OA and THA*

	Without *adjustment for BMI*				With *adjustment for BMI*			
	Hip OA		**THA**		**Hip OA**		**THA**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Type of Shift Work								
None	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Only Day Shifts	1.07 (0.92-1.24)	0.369	1.04 (0.96-1.13)	0.363	1.04 (0.90-1.21)	0.565	1.02 (0.94-1.11)	0.652
Night Shifts	1.02 (0.87-1.20)	0.813	0.98 (0.89-1.07)	0.586	0.98 (0.83-1.16)	0.828	0.94 (0.86-1.03)	0.216

All models adjusted for age, sex, education, race, Townsend Deprivation Index, and frequency of manual/physical labor. HR=Hazard Ratio