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Cortisol and shiftwork: A scoping review

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SUMMARY

The aim of this review was to explore the extent and nature of evidence exploring shiftwork and disruptions to cortisol. A systematic search was conducted across five databases: Medline, EMBASE, Psych INFO, Joanna Briggs Institute and PubMed between July-August 2020. Cortisol data were characterised into three main outcomes, 1) cortisol levels, 2) cortisol rhythm, and 3) cortisol awakening response (CAR) during shiftwork. Main findings demonstrate that shiftwork, especially night shift, significantly disrupts production of cortisol, the cortisol rhythm and CAR and, irregular shift schedules produce greater disruptions to cortisol than regular shift schedules. It was difficult to draw conclusions about the impact of shiftwork on movement of the cortisol rhythm and adaptation or recovery of the cortisol rhythm to and from night shift as the literature lacks consistency in definition of methods and variables. The present state of literature demonstrates cortisol levels, cortisol rhythm and the CAR are all disrupted by shiftwork, but there is a lack of consistency between studies on use of variables and most of the literature focuses on acute disruption rather than chronic effects. It will be important for future studies to investigate possible mechanisms that link shiftwork, disruptions to cortisol and chronic health conditions prevalent in shiftworkers

Key Words: Shiftwork, Cortisol, Cortisol Awakening Response (CAR)

Introduction

Shiftwork permits business to maximise production by enabling operations (e.g., medical, mining, manufacturing) to function around the clock. While shiftwork has become a fundamental part of many industries generating numerous advantages, there are disadvantages, such as negative impacts on physiological functioning due to disrupted daily (circadian) rhythms [1–3]. For this review, shiftwork includes any work schedule occurring outside 'traditional' work hours (0900h-1700h) [4]. Shiftworkers may work permanent or rotating shifts in a variety of combinations, desynchronising biological and social rhythms. Changes in the circadian rhythm of hormonal markers, such as cortisol, have provided a physiological approach to assess shiftwork-induced disruptions[5].

Cortisol is secreted by the hypothalamic-pituitary-adrenal (HPA) axis, a key endocrine and stress response system [6, 7]. Cortisol levels are continuously monitored in the body to maintain homeostasis. Cortisol regulates its own secretion via negative feedback whereby high levels of circulating cortisol prompt the secretion of corticotrophin-releasing hormone and adrenocorticotropic hormone to be suppressed, which in turn moderates the production and release of cortisol [8, 9]. Cortisol displays a distinct circadian rhythm that aligns with the daily circadian rhythm of the HPA axis, which is regulated by the body's central clock, the suprachiasmatic nucleus [10]. Cortisol levels begin to slowly rise ~2-3h after sleep onset, reaching a peak early in the morning (~0900h) with levels steadily declining across the day, until reaching a nadir around midnight when HPA axis activity is also at its lowest [10–12]. The diurnal profile can be masked by stress induced cortisol surges, (e.g., food intake, anxiety producing stressors) [8, 12]. Under normal physiological conditions, the cortisol rhythm is constant and reproducible however, some individuals (~10%) exhibit a flattened almost non-linear diurnal rhythm the determining factor/s of which are unknown [13, 14].

Morning cortisol levels show a sharp increase (~50-75%) that typically peaks ~ 30-45-minutes post awakening (cortisol awakening response–CAR) [15, 16]. CAR is a distinct feature of the cortisol circadian cycle [8, 17]. It is considered to be an independent dynamic event initiated by awakening rather than a continuation of normal diurnal cortisol profile [18]. In contrast to the secretion of cortisol throughout the day, CAR is regulated by neural input from the sympathetic nervous system stimulating the adrenal cortex which fine-tunes the CAR response [19]. Different patterns of CAR (e.g., blunted, and heightened peaks), have been associated with a range of negative health outcomes (e.g., post-traumatic stress disorder, depression) [20, 21]. However, the relationship between CAR and underlying physiology of these condition is unclear [8]. The role of CAR is similarly unclear, though research suggests it to be associated with adverse prior day experiences and anticipation of forthcoming challenges [22, 23]. Researchers have further suggested CAR, may play a role in immune system balance. It has been proposed that CAR may be the event that switches the immune system from a night-time cellular to a day-time humoral response immunity [8, 24]. CAR is frequently used in psychoneuroendocrinology as a biomarker of HPA axis activity [8, 12].

Glucocorticoid receptors, the receptor to which cortisol binds, are present in virtually all tissues in the body. Cortisol, therefore, can affect the performance of nearly every organ system. [25, 26]. Cortisol plays a central role in the regulation of metabolism [10], promotes the breakdown of carbohydrate and protein [27, 28] is an important regulator of immune and inflammatory processes [29], and regulates blood pressure [27]. Health problems arise if cortisol levels are too high or too low. Through the process of allostasis [30] the body continuously monitors and adjusts cortisol levels to ensure stability and balance. An allostatic state (e.g., a flattened cortisol rhythm following consecutive night shifts) is the result if

stability is not retained [31]. Chronic instability e.g., cortisol levels repeatedly elevated over many days, results in allostatic overload leading to increased disease risk [31].

Significant disturbances on the diurnal cortisol rhythm have been associated with pathologies such as depression and obstructive sleep apnoea [10]. Research further suggests that persistent disturbances in the cortisol rhythm, which shiftworkers regularly experience, may play a role in the pathogenesis of health burdens such as cardiometabolic disease and cardiovascular disease [32–34]. These health problems translate into higher economic and social costs for the individual, organisations and society [35]. The aim of this scoping review was to explore the extent and nature of evidence concerning the impact of shiftwork on cortisol.

Method

Adopting Arksey et al. [36] and Levac et al.'s [37] guidelines a comprehensive scoping review on literature relating to shiftwork and cortisol was undertaken.

- **Search dates:** July-August 2020
- **Key search terms:** "shiftwork" or "night shift" or "work hours" and "cortisol" or "salivary cortisol" or "cortisol awakening response" or "CAR" and "cortisol rhythm" or "circadian misalignment" and "sleep loss" or "sleep deprivation" or "sustained wakefulness
- **Electronic databases:** MEDLINE, EMBASE, Psych INFO, Joanna Briggs Institute, PubMed.
- **Inclusion criteria:** Human studies with both field and/or experimental (simulated) designs investigating associations between shiftwork (i.e., work

outside of the normal 9 am-5 pm hours); Sleep restriction, sleep loss, disturbed sleep; Changes in cortisol levels/rhythms; the CAR; Healthy adults

- **Exclusion criteria:** Use of hair and urinary cortisol (usually assessed as a 24h total, which do not capture diurnal fluctuations or rhythmicity [85,86]); Interventions e.g., dexamethasone, light, that significantly influence cortisol levels. Light increases morning cortisol levels [38]; dexamethasone reduces cortisol levels by suppressing the HPA axis. If shiftworking individuals displayed elevated morning cortisol levels post dexamethasone intervention, this would intimate a disturbance in the functioning of the HPA axis rather than shiftwork i.e., circadian disruption, influencing cortisol levels [39, 40]
  Conference/symposium papers; Exploring Psychological illness and cortisol; Exploring Neurological illness e.g., Parkinson's, Alzheimer's, etc; Exploring sleep patterns, cortisol etc in children; Examining differences between a clinical population and shiftworkers

The literature search identified 6,486 papers of which 1,728 duplicates were removed. The remaining 4,758 papers were reviewed twice against title and abstract by LG, SK, JD and SB. Following consideration of the inclusion and exclusion criteria 158 papers were selected and assessed for full-text eligibility, with 38 satisfying the criteria for this review. Article selection followed standard processes [41] and is illustrated in Figure.1. Papers were included if they described published/unpublished primary research or literature reviews that included shiftwork and cortisol. All studies that reported an association between shiftwork and cortisol, irrespective of study design were eligible for this review. If the relevance of a study was unclear from the abstract, these papers were selected and assessed for full-text eligibility. During the process of study selection, numerous studies were excluded. Examples

include studies that used hair or urinary cortisol or interventions such as dexamethasone. Papers that had poor or no methodological details or were not specific to shiftwork and cortisol were excluded from the scoping review. Any uncertainties about inclusions and exclusions were discussed between LG and SB. Reference lists of identified articles were scanned to detect additional papers that may have been missed during the initial electronic database searches. None were identified. A summary of included papers is provided in Table 1.

Key information was harvested as per the guidelines suggested by Arksey et al. [36]. A wide variation of terminologies has been used in the literature to report outcomes (e.g., profile, levels, rhythm, acrophase, slope). Cortisol measurement approaches in each paper were grouped into one of the three categories.

1. **Cortisol levels:** Where articles compared and/or reported differences in cortisol levels at time-points specified by clock time, minutes post activity, time into shift (e.g., start versus end)
2. **Cortisol rhythm:** Where articles reported changes in diurnal shape/pattern or profile, reporting variations observed in amplitude, peak and trough times, phase shifts, normal or reversed rhythms.
3. **Cortisol awakening response (CAR)**: Where articles reported waking levels, morning peak, Mean Increase (MnInc) and or Area Under the Curve (AUC)

Figure 1
PRISMA flow diagram for article selection

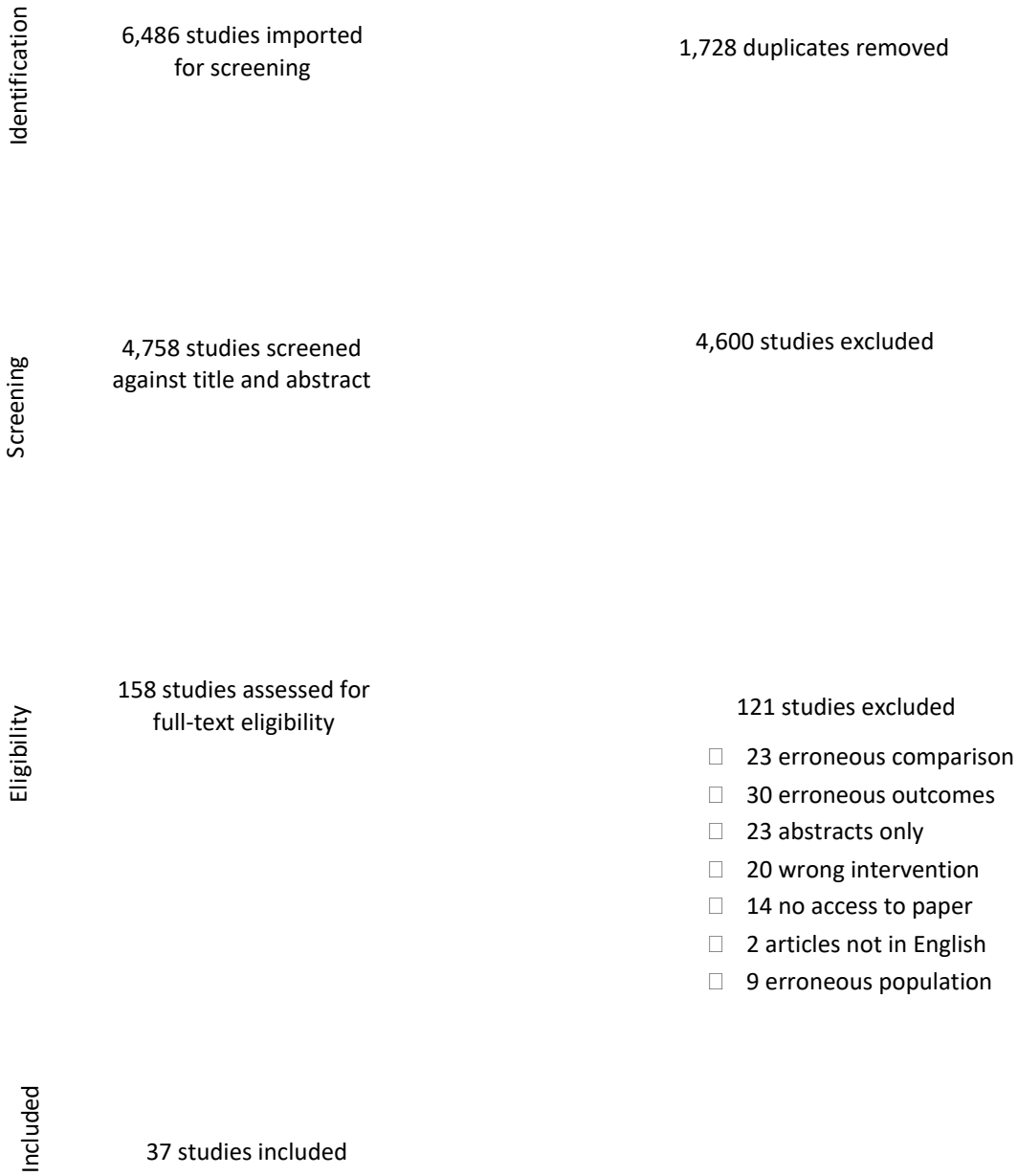


Table 1
Research studies in review

First Author[ref]	*n*	Sample	Cortisol Primary(P) Secondary(S)	Exposure	Days, Sample	Sample times	Outcome		
							Level	Rhythm	CAR
Cannizzaro et al. 2020 [45]	90	Security	S	NS in monitoring room $_{vs}$ NS inspecting streets $_{vs}$ DS	1,3	2200h,0630h, 1400h	↑ in both NS conditions		
Choshen et al. 2020 [47]	51	Doctors	S	26h-NS (Residents) $_{vs}$ no NS (Attendings)	2, 2-4	D1 0800h-1000h for no-NS & start of 26h-NS. D2 0800-1000h post 26h-NS only	↑ after 26h-NS		
Hall et al. 2019 [68]	26	Firefighter	P	OC+callout $_{vs}$ OCnocallout $_{vs}$ NOC	7,7	Waking +30, +60-min, 3h, 6h, 9h and 12h post-waking	↓ AUC_g OC+callout		↓ peak OC+callout
Morales et al. 2019 [53]	58	Doctors	S	24h-on-call $_{vs}$ DS	1,2	0800h start of workday for both conditions & 0800h morn post 24h-on-call	↑ post 24h on-call		

Vincent et al. 2019 [79]	72	Firefighters in lab	S	OC+callout vs OCnocallout vs Control (not OC)	3,9	0700h,0715h, 0730h, 0745, 0800h, 0930h, 1230h, 1430h and 1730h	↓ AUC_g in OC conditions		AUC ↓ in OC+callout peak ↑ in OCnocallout
Li et al. 2018 [63]	70	Doctors	P	Physicians working SW or daywork only. Assessed at BL (2 consecutive days not during or on days post NS) and 12mth follow up; same procedure as BL	4,4	Waking, +4h, +8h and +16h	↑ AUC_g in SW	↑ slope in SW	Waking levels sig higher in SW group
Chang 20018 [71]	128	Nurses	S	Slow-rotating shift: 1-mth DS, 1-mth ES, 1-mth NS. Assessed in each shift-type	3,2	Waking +30min. Data collection started day-14 of new roster to eliminate shift change influence			DS sig ↑ CAR compared with ES & NS. DS sig ↑ waking levels compared with NS
Charles et al. 2016 [59]	319	Police	P	Fixed-shifts 4-days-on of either DS, ES or NS followed by 4-days off	1,7	Waking, +15, +30, +45min post-waking, at lunch, dinner & bed (times not defined)	Levels differed between shift-type (data not provided)	↓ slope in NS	
Hall et al. 2016 [54]	16	Lab	S	OC+callout during day vs OC+callout at night vs	4,7	Waking +15, +30, +45 & 60min post-	↑ in OC+callout at night. No		

				OCnocallout (day & night)		waking + 90min & 120min	difference in OC+callout during day	
Jensen et al. 2016 [50]	73	Police	S	Compared 2, 4 & 7 consecutive NS with = recovery days	2,6	Last day of NS and last day of recovery. First sample on waking, last sample at bed. Remaining samples collected at 0700h, 1100, 1500, 1900, 2300, & 0300h only if awake. 1100h & 0300 samples excluded from analyses	↑ levels post-waking in all 3 conditions, a drop & rise again at bedtime.	Phase delay in each condition
Wolkow et al. 2015 [57]	37	Firefighters	S	3-days & 2-nights simulated firefighting work. SR(4h-TIB) $_{vs}$ NoSR(8h-TIB)	2,6	Waking (0630h), 0730h, 0900h, 1115h, 1330h, 1530h, 1730h, 1930h, 2130h.	↑ in SR at 1730h and 1930h on day-2 and at 1530h, 1730h, and 2130h on day-3. AUC ↑ in SR on day-2 and day-3	

Lammers et al. 2015 [76]	25	Police	P	Assessed once in academy working (0800h-1600h) and 3 times post academy working rotating SW schedule; DS, ES & NS (no information on what shifts officers worked at follow-up)	4,3	Waking, +30min, +60min post-waking			Mean values ↑ from baseline to sig higher levels at ~14mths after starting SW
Merkus et al. 20015 [67]	29	Oil rig	P	Two-weeks 12h shift tours of either 14-DS or 14-NS	4,3	Waking, +30min post-waking and bedtime on the 1st, 4th, 7th & 11th-day off shift	NS sig smaller decline to evening levels on day-4 and day-11	NS sig flatter cortisol profile on 1st day off	NS decreased waking levels and post 30min on day-4 and 7 post- roster
Niu et al. 2015 [42]	62	Nurses	P	5DS+5off vs 5NS+5off vs 4DS+2off vs 4NS+2off	9,4	Days-2-5 on shift and days-1-5 off shift. Waking, +30min, 6h and 12h post-waking	↑ levels 6h and 12h post-awakening in NS	Reversed rhythm by day-4 on shift in NS. Rhythm restored by day-2 off roster in NS	Days-3-4 on shift NS blunted CAR.
Ernst et al. 2014 [48]	30	Doctors	S	1x24h-OC vs 1 x NOC	2,2	Bloods before-and-after	Morning post 24h-		

						OC/NOC at 0700h & 0900h.	OC cortisol levels ↓ compared to morn before		
Guyon et al. 2014 [58]	13	Healthy participants	P	2SR(4h_TIB) vs 2NoSR(10h_TIB)	1,45	Blood and saliva at 20-min intervals from 0900h-0000h and 1400h-0000h	SR displayed↑ in total cortisol levels	Amplitude across the day ↓ by ~21% in SR	
Bostock et al. 2013 [74]	30	Pilots	S	2DS vs 2ES + 2-rest-days	2,6	Waking +30min, 2.5h, 8h, 12h and Bedtime	↑ AUC in DS with slower rate of decline compared with ES and rest-days		CAR greater in DS. DS ↓waking levels & greater peak at 30min
Fekedulegn et al. 2012 [72]	65	Police	P	DS, ES, or NS	1,4	Waking +15, +30 and 45min post-waking	Levels differed sig at all time-points between shift-type. Total AUC lowest in NS		NS ↓ waking levels. CAR peak smaller in NS
Anjum et al. 2011 [43]	16	Nurses	S	Continuous 9-days NS with alternate DS. # Of NS and DS during 9-day schedule not provided	# Of sample days not advised	~8h intervals on a NS 1300h-1500h, 2200h-0100h, 0500h-0800. On a DS	NS ↓ early morning, ↑ at midnight and highest in the afternoon	Altered pattern during NS	

						1400h-1500h, 2100-22h, 0500h-0600			
Carev et al. 2011 [46]	12	Doctors	S	Each participant observed on an 8h-DS and again on a 24h-shift	2,6	0800h, 1100h, 1400h, 1700h, 2100h, 2300h	Both conditions ↑ levels at 2300h.		
Wirth et al. 2011 [73]	68	Police	P	Long-and short-term SW. 4-days on, 3-days off, 3-days on, 3-days off. DS, ES or NS.	1,4	On a scheduled day-off. Majority worked a DS or a day-off prior to sampling day. Waking +15, +30, +45min post-waking			Waking cortisol AUC ↓ in short-term NS and ES than DS
Ulhôa et al. 2011 [69]	42	Truck drivers	S	DS (0800h-1800h) vs Irregular shift (2030h-~0800h) Irregular shift could also work a MS or AS in the same week (start and end times not provided)	2,3	Working-day and a day-off. Waking, +30min and bedtime.	Irregular shift ↑ levels on days-off compared to DS		CAR ↑ on workdays in both conditions compared to day-off
Harris et al. 2010 [49]	19	Oil rig	S	BL data: 14-days 12h fixed shift; either NS 1900h-0700h or DS 0700h-1900h. Follow-up data	7,5	2 days off-roster 1-week before roster and 1-week post roster. During roster	Bedtime sig ↑ post 1st NS	Flat on day-one of swing-shift. Swing-shift	CAR after 1st NS sig ↓ Day-one and last-day of swing-shift CAR ↓ compared to

				~9mths after workers transitioned to Swing-shift (7xNS and 7xDS)		on fixed shifts day-2, 7, and 14. During swing-shift on day-2 of NS, last night of NS, day-one after rotating and last day. Waking, +30min, 6h, 12h and bedtime.		rhythm readapted 1-week post roster. No readaptation in Fixed NS rhythm 1-week post roster	when working fixed DS
Korompeli et al. 2009 [56]	32	Nurses	S	Fixed MS only $_{vs}$ Irregular-rotating schedule (MS, ES & NS)	1,2	Bloods at start and end of MS shift. Bloods also at start and end of ES and NS in Irregular schedule	Irregular schedule sig greater reduction in cortisol levels		
Thomas et al. 2009 [52]	7,196	Shiftworkers	S	Regular NS 2200h-0700h at least once-a-month	1,2	45mins post-waking, +3h post-waking	↑ levels 45min post-waking		
Griefahn et al. 2008 [77]	16	Healthy participants	P	Experimental SW: 3xDS$_{vs}$ 3xNS	3,19	24h-phase-assessment post 3xDS and post 3xNS. 0700h after night-sleep and 1500h after day-sleep +			CAR sig ↑ after night-sleep (DS)

						half-hrly during SW and hrly during 24h-phase-assessments			
Vangelova et al. 2008 [55]	25	Sound engineers	S	Forward-rotating-schedule (MS, AS, ES, Rest, NS, Rest) vs Backward-rotating schedule (ES, AS, MS, NS, Rest, Rest) Same start and end times for shifts in each schedule.	4,3	MS 0600h, 0900h, 1200h; AS 1200h, 1500h, 1800h; ES 1800h, 2100h, 2400h; NS 2400h, 0300h, 0600h	Backward schedule ↑ levels at 0900h in MS and at 0300 NS		
Dettenborn et al. 2007 [78]	13	Healthy participants	P	SR. 3xNightly waking's at different times during the night (disturbed sleep) vs no disturbed sleep	3,2	Waking, +15mins on each nightly waking and each morning.	Slight ↑ on 3rd waking		No difference in morn CAR between conditions
Kudielka et al. 2007 [66]	102	Factory workers	P	Permanent NS and DS (MS and ES) moving to Forward-rotating Schedule. Some workers remained on permanent NS or DS	2,8	Permanent NS, on nights 1 and 5 of 6 consecutive NS and 2nd free-day. Permanent DS, 2nd MS and 2nd ES and 2nd free-day. Forward-	AUC for NS sig smaller than MS and ES. NS profile attenuated in perm DS who moved to Forward-rotation	Blunted profile during roster and days-off in perm NS. Profile stable in perm NS workers	Former permanent DS who moved to Forward-rotation ↓ CAR

						rotation 2nd day of each shift. Waking, +30, +45, +60min, +4h, +8h, +12h, +16h.		switching to Forward-rotation	
Karlson et al. 2006 [64]	296	Factory workers	P	24h-Fast-forward (MMAANN) vs permanent daywork or weekly changing schedule of 0600h-1400h and 1400h-2200h	2,5	Day-2 of a MS or AS and 3rd day-off. Waking, +30min, 1100h, 8h post-waking and ~2100h	MS ↓ mean levels across the day.		MS ↓ waking levels and ↓ peak
Lac et al. 2004 [5]	32	Factory workers	S	Dayworkers vs 2 different rotating schedules (3-days-on, 2-days-off, 3/2 and 7-days-on and 5-days-off 7/5)	1,8	Dayworkers assessed on day-4 and for SW on day-3 following a change. Every 2hrs from waking till bedtime	7/5 showed an earlier rise in levels	Both 7/5 & 3/2 disrupted profile during NS.	
Federenko et al. 2002 [75]	51	Nurses	P	Compared MS, ES and NS.	2,4	1st and 2nd day of MS, ES and NS. Waking, +30, +45, +60min	Sig ↑ in ES and NS		ES levels continued to↑ over the 60min sample period. CAR most distinct in MS.

Hennig et al. 1998 [60]	24	Nurses	P	$N_{vs}D$	9,9	2 consecutive MS then 7 consecutive NS. MS sampled 0600h, 1200h, 1800, 2100h. NS sampled 2100h, 2400h, 0300h, 0600h	Morning levels lower than evening levels.	Pattern change seen after 4th NS. Full reversal after 5th NS
Weibel et al. 1996 [61]	11	Shiftworkers	P	NS_{vs} Dayworkers	~2, 10min interval	NS workers in lab for ~40h after 4-5 consecutive NS. Blood draws 10min-intervals from 2000h (day-one) to 2300h (day-two)		Acrophase shift of ~6.5h. Quiescent period shift of 3h.
Roden et al. 1993[62]	9	Shiftworkers	S	NS_{vs} Dayworkers	1,1h int	NS workers in lab after 5-6 consecutive NS. 1hrly bloods from 0900h (day-one) to 1000h (day-two)		NS no phase shift evident
Motohashi 1992[65]	7	Ambulance	P	DS_{vs} 24h-shift	1, ~4hrly	~4h intervals and ~30min post ambulance		Phase advance by ~2hrs in 24h

						activities for 24h. Times for DS not specified.		
Fujiwara et al. 1992[51]	6	Healthy participants	S	Participants exposed to 2 consecutive DS, ES & NS. 1-week interval between each shift experience	6,4h int	2ml blood draws 4hrly.		Sig phase delay in ES. Second peak seen at 1600h during sleep in NS
Touitou et al. 1990[44]	4	Oil refinery	S	Long-term Rapid-rotation SW assessed during NS and compared with Dayworkers synchronised with lights on 0700h and off 2300h	1,4	2hrly bloods during NS (0000h-0800h). Dayworker bloods same time as NS	Sig ↑ in SW between 0000h-0200h. Dayworker levels ↑ between 0200h-0800h but not in SW.	Amplitude ↓ in SW

Note. Cortisol 1 or 2, 1=primary outcome, 2 = secondary outcome, Day, Samples, 1st# = #of sampling days, 2nd # = # of samples per day, CAR=cortisol awakening response, NS=nightshift, DS=dayshift, ES=evening-shift, MS=morning-shift, OC=on-call, NOC=not-on-call, SR=sleep-restriction, SW=shiftwork, NoSW=No-shiftwork, collection method saliva unless otherwise noted, ↑=increase, ↓=decrease

Findings

The 38 included studies were published between 1990 and 2020. The majority were from Europe, with the greatest number from Germany. More papers were published in the last 10 years (23 papers) compared with the previous two decades combined, with a relatively even spread of contributors from Asia, Europe, North America and Oceania (Australia). Approximately half of the studies focussed on first responders and medical personnel (Table 1). Six papers were laboratory experiments simulating shiftwork hours. The majority of studies explored shift type or scheduling (see Table 2 for shift schedules). Four papers examined sleep restriction (partial or complete loss of sleep, often a result of inadequate opportunity, sub-optimal sleeping conditions, and/or time-of-day) [38]. Cortisol was the primary outcome in 17 papers (measured via saliva=14, blood=1 or blood+saliva=1), and the secondary outcome in 21 papers (measured via saliva=16, or blood=6). The majority of studies (30 papers) were conducted in the field with sampling conducted by participants. Eight studies were conducted in a laboratory, with sampling conducted by researchers. The majority of studies employed ≥3 sampling time points with six studies collecting samples at two time points only. Nineteen studies collected samples on awakening.

Overview of the outcome reported

The results of the studies will be presented by outcome: 1) cortisol levels, 2) cortisol rhythm and, 3) CAR.

Cortisol levels

Night Shift

Studies explored either the acute effects of night shift or the effect of multiple night, consecutive nights. In the studies exploring the acute effects, two reported that salivary cortisol levels in night shiftworkers were lowest in the morning, high in the afternoon and increased in the evening and at midnight [42, 43]. Other studies reported specific time points across the night based on sampling times. Touitou et al. [44] found serum cortisol levels were significantly higher in shiftworkers on an nightshift between midnight and 0200h compared with dayworkers. Cannizarro et al. [45] found cortisol levels were significantly increased at the start (2200h) and end (0630h) of a night shift compared with the start and end of a day shift. Similarly, Carev et al. [46] reported high salivary cortisol levels at 2300h in individuals working 24h shifts. Moreover, in a study examining medical staff regularly working a 26h shift (4-8 times per month), Choshen-Hillel et al. [47] posited individuals regularly working 26h shifts during their medical residency were chronically sleep deprived. Medical residents at baseline (post 3-nights of normal sleep) displayed morning cortisol levels that were lower compared to individuals who did not work these shifts. On the morning following a 26h shift, morning cortisol levels of medical residents rose to levels similar to individuals who did not work these shifts. Similarly, Ernst et al. [48] found morning cortisol levels in doctors were lower after a night on-call compared to the morning before and with doctors not on-call.

Four studies assessed the influence of consecutive night shifts. Niu et al. [42] found, when individuals worked five consecutive night shifts, the day-to-day levels of cortisol between days 2 and 4 exhibited lower fluctuations than individuals working five consecutive days shifts. Harris et al. [49] found cortisol levels before bed were significantly higher after first night shift, however after working 12 consecutive night shifts cortisol levels at bedtime (i.e.,

morning) were similar to bedtime levels (i.e., night) in day shiftworkers but the level of decrease was low compared to day shift. Additionally, Jensen et al. [50] compared the effect of two, four and seven consecutive night shifts with an equal number of recovery days and found all three conditions induced changes to cortisol levels. Following two nights on and two nights off, the lowest levels of cortisol were observed at 8h post awakening, 9.23h post awakening following four nights on and four nights off and at 11.31h post awakening after seven nights on and seven nights off. However, one short term experimental study provides contradictory results reporting the 2-day mean cortisol level during the night shift did not increase significantly [51]. In a longitudinal investigation of individuals who were part of a British birth cohort study (n = 7,916), it was found that people who regularly worked night shift hours had significantly higher cortisol levels 45mins and 3h post awakening [52].

Ten studies investigated the acute effects of night shift and consecutive night shifts on cortisol. All except one study found that afternoon and night cortisol levels were increased. Additionally, the more consecutive night shifts individuals work the longer cortisol levels remain higher post awakening.

Shift Schedules

A number of studies explored shift schedules and the influence of transitioning between shift types. Working on-call over night with call outs, two studies observed participants exhibited increased levels of basal cortisol [53, 54] compared to individuals working day shift and on call where no significant changes occurred in cortisol levels following a day call out [54]. Lac & Chamoux [5] found individuals working a slow-rotating schedule (7-days on, 5-days off,7/5) displayed an earlier rise in cortisol, at 0500h compared to 0700h in individuals working a fast-rotating (Table 2) schedule (3-days on, 2-days off,3/2).

Cortisol levels were significantly higher during a night shift (2300h-0900h) in the 7/5 group compared to the 3/2 group. Vangelova et al. [55] found individuals working a backward-rotating (Table 2) schedule demonstrated higher levels of cortisol at 0900h during a morning shift and at 0300h on night shifts compared to individuals working the same shifts on a forward-rotating (Table 2) schedule.

Personnel who transitioned to a swing-shift schedule demonstrated higher bedtime values and a lower level of cortisol decrease during the week of day shift compared to when they worked a permanent day shift schedule [49]. In contrast one study found when individuals transitioned from night shift to a day shift the levels of cortisol increased slightly during the day however the increase in cortisol levels were considered significant clinically but not statistically [43]. Conversely, another study reports the mean reduction of cortisol levels between the start and end of shift was statistically significant for individuals transitioning between consecutive morning, evening and night shifts on an irregular shift schedule [56].

The literature regarding shift schedules and cortisol levels presents varied findings depending on the shift schedule explored. Although reported cortisol levels whilst working the night shift were consistent with night shift specific studies (i.e., higher levels at night and lower levels in the morning), the varied changes reported in cortisol levels overall suggest that irregular shift schedules rather than the shift type itself may influence the observed changes in cortisol levels.

Table 2
Shift schedules

Term	Schedule	Shift times
Backward rotating	EAMN/RR	E=1730h-0030h, A=1130h-1930h, M=0530h-1330h, N=0000h–0600h
Forward rotating	MAE/R/N/R	M=0530h-1330h, A=1130h-1930h, E=1730h-0030h, N=0000h–0600h
24h fast-forward rotating	M/M/A/A/N/N RRRR	Shift changes at 0600h, 1400h and 2200h
Fast rotating	MMM/RR EEE/RR NNN/RR	M=0400h-1200h, E=1200h-2000h, N=2000-0400h
Slow rotating	MMM/EE/NN/RRRRR/ MM/EEE/NN/RRRRR/ MM/EE/NNN/RRRRR	M=0400h-1200h, E=1200h-2000h, N=2000-0400h
Rapid-rotating	MMEENN/RRR	M=0600h-1400h, E=1400h–2200h, N=2200h-0600h
Irregular schedule	MEN any combination over an irregular time-period	M=0700h-1500h, E=1500h-2300h, N=2300h-0700h
Swing shift	14-day (7N/7D)	N=1900h-0700h D=0700h-1900h

Note: M=morning, A=afternoon E=evening, N=night, R=rest-day; [5,46,51,57,66,68]

Sleep Restriction

A small number of studies assessed the relationship between sleep restriction and cortisol levels. Two studies found a significant influence following two consecutive days of sleep restriction (4h time-in-bed) [57, 58]. Sleep restriction is associated with significantly higher total cortisol levels as measured via area under the curve (AUC), with late afternoon and evening levels significantly elevated [57, 58]. Wolkow et al. [57] reported that after two days of sleep restriction cortisol levels at the clock times of 1530h, 1930h & 2130h were higher than at these same time points on the day before exposure to sleep restriction. Guyon et al. [58] found total serum cortisol levels were increased by ~21% and evening cortisol levels increased by ~30% after two days of sleep restriction.

There are a limited number of papers exploring sleep restriction in shiftworkers and cortisol. Findings suggest that acute sleep restriction influences cortisol levels in a similar way to that of working ~7 seven consecutive night shifts. That is cortisol levels remain significantly higher for longer across the day post awakening. Irregular shift schedules may exacerbate chronic sleep restriction and associated long-term disrupted cortisol levels. Additional and larger studies conducted over more than two-days are needed to advance knowledge on the magnitude of change in cortisol levels that occur the longer sleep restriction occurs.

Cortisol Rhythm

Night shift

A total of eight studies assessed consecutive night shifts and adaptation of the cortisol rhythm [42, 43, 49, 50, 59–62]. Three studies [42, 60, 61] found there was a clear reversal in the cortisol rhythm (i.e., high levels at night which would normally be low and low levels in the morning which would normally be high), after five consecutive night shifts. Hennig [60] and Niu et al. [42] determined that markedly increased levels at the same time points (e.g., 2100h and 0600h or 6h and 12h post awakening) indicated reversal of the cortisol rhythm. However, Weibel [61] determined a phase shift of ~3h in the quiescent period and ~6.5h in the acrophase indicated a change in the rhythm and therefore an adaptation to night shift. Harris et al. [49] determined the cortisol curve was an indicator for changes in the diurnal rhythm and that individuals adapt to night shift within seven-days; the cortisol rhythm of night shiftworkers was closer to normal day values by the seventh-day of night shift.

Two studies [43, 59] showed that the percentage of hours worked on a night shift i.e., where night shift was the dominant shift type in their schedule, altered the cortisol circadian pattern. Charles et al. [59] reported that night shiftworkers had a significantly flatter diurnal cortisol curve compared with day shiftworkers. In contrast to this Anjum et al. [43] found some individuals working long term night shift on a nine-day roster where night shift was the dominant shift displayed a normal rhythm during night shift. However, when the shift rotated to a day shift a slightly reversed, but not significant, pattern was found. They concluded that alteration in the circadian pattern may develop later when the shifts were rotated.

In contrast to the above studies two papers [50, 62] report no reversal of the cortisol rhythm or evidence of its adaptation to night shift. Jensen et al. [50] compared the effect of

two, four and seven consecutive night shifts with an equal number of recovery days. Findings demonstrated significant differences in the cortisol rhythm on all three interventions with an increasing phase delay evident with the increasing number of night shifts by ~33 minutes per day. However, Jensen et al. [50] determined there was no adaptation of the rhythm to night shift, even after seven consecutive nights, as the curve of the cortisol rhythm did not follow the same diurnal rhythm in relation to sleep as it did on recovery days. Roden [62] exploring night shiftworkers after their fifth or sixth consecutive night shift against day workers found the acrophase for night shiftworkers to be similar to that of day workers, and the majority of night shiftworkers showed no evidence of a discernible phase shift of the cortisol rhythm when compared to day workers.

The literature on shiftwork, specifically night shift and changes in cortisol rhythm is limited to a small number of papers each with its own interpretation of when or if the cortisol rhythm adapts to night shifts. It was difficult to compare these studies due to the selection of different outcome measures to describe changes in cortisol and different statistical techniques for analysis. Thus, as a field choosing the same outcome measure to determine reversal or adaptation of the cortisol rhythm would help to clarify the occurrence of this shiftwork induced phenomena.

Shift Schedules

Several studies explored the impact of shift schedules and mixed findings have again emerged. Li et al. [63] compared doctors working shift with doctors working days only and found cortisol levels at baseline significantly predicted a steeper slope, large AUC of diurnal cortisol and significantly higher waking levels 12-months later. Touitou et al. [44] investigated the relationship between a fast forward rotating shift schedule changing every

three to four-days and found this schedule induced changes to the peak and trough and decreased the amplitude of cortisol with no apparent phase shift. In contrast Karlson et al. [64] found individuals working the early morning shifts (starting 0600h) on a 24h fast-forward rotating shift (Table 2) schedule clearly showed an altered rhythm with a forward adjusted phase shift compared with regular daytime workers. Lac and Chamoux [44] comparing a fast-rotating schedule with a slower-rotating schedule reported the acrophase moved from 0800h to 1100h in the fast schedule and occurred earlier in the slower schedule moving from 0700h to 0500h. Investigating sustained operations Guyon et al. [58] and Motohashi [65] both reported alterations in the phase and amplitude of the cortisol rhythm. Fujiwara et al. [51] reported decreased amplitude in experimental short-term evening and night shifts. In contrast, other studies report the amplitude remains unaffected [50, 61, 62]. Switching workers to a fast-rotating (Table 2) schedule Kudielka et al. [66] found the cortisol profile in permanent night workers did not differ significantly however, permanent day workers initially displayed a significantly blunted cortisol profile that normalised after a short adjustment period.

In summary six different types of shift schedules had been investigated. Similar to results reported for shift schedules and cortisol levels the diverse changes reported with regards to changes in the cortisol rhythm overall suggest that irregular shift schedules rather than the shift type itself may influence the observed changes in the cortisol rhythm.

Recovery

There is evidence that shiftwork, specifically night shift, can induce disruptions to cortisol however, some of the studies reporting adaptation of the rhythm report mixed results on recovery of the rhythm. Harris et al. [49] exploring 14-days of night shift and 14-days of

swing-shift (Table.2) found that although the cortisol rhythm in workers on both schedules adapted to night shift after seven-days, recovery of the rhythm for those working 14 consecutive night shifts had not returned to baseline values after 7-days off roster. Additionally, the cortisol rhythm of workers on a swing-shift (Table.2) was flat on the first day rotating from night shift to day shift but started to revert toward a normal rhythm during the week of day shift and was completely readapted to normal values after 7-days off roster. A similar study by Merkus et al. [67] reported that on day one off roster following 14 consecutive night shifts, night shiftworkers showed a flatter cortisol profile, but no flattened profile was evident on day-seven when compared to their baseline profile. Although the diurnal profile was evident from day-seven the cortisol profile had not recovered, that is, did not reflect its baseline profile by day-11 off roster.

Following five consecutive night shifts Niu et al. [42] found the cortisol slope of night shiftworkers compared to day shiftworkers on day one off roster displayed significant differences at +30min post awakening to 6h and 12h post awakening. However, on day-two off roster, both night and day shiftworkers displayed similar cortisol profiles suggesting the cortisol profiles in night shiftworkers was restored. They further concluded that personnel working night shift require at least four-days for the cortisol rhythm to readapt. Karlson et al. [64] however, reported that partial adaptation of the cortisol rhythm to night work did not readapt after four-days off. Additionally, Jensen et al. [50] comparing the effect of two, four and seven consecutive night shifts with equal number of recovery days reported there was no significant difference between the number of night shifts in the rhythm of cortisol on recovery days.

There are few studies reporting on the recovery of the cortisol rhythm and what this looks like following shiftwork induced disruption. The lack of research and data in this area raises questions about the recovery of the cortisol rhythm, what it actually looks like and potential effects on health. Thus, similar to adaptation or reversal of the rhythm, as a field, choosing the same outcome measure to determine reversal or adaptation of the cortisol rhythm would help to clarify the occurrence of this shiftwork induced phenomena.

The Cortisol awakening response (CAR)

Sixteen studies explored the association between shiftwork and CAR (the vigorous increase seen in cortisol levels immediately after waking, with levels peaking ~30-45-minutes post-awakening). Ten studies were conducted in the field. Of the field studies, two used objective verification of awakening time (i.e., wrist actigraphy) [68, 69] and texting participants the night before sampling occurred the following day to maximise adherence to the sampling schedule [67]. The remaining field studies used self-report measures (sleep diary or collection diary) for the collection and timing of samples. Validity of data collection, particularly in field studies, relies on participants accurately following a timed sampling schedule, which begins with the moment of awakening. Inaccurate sample timing can occur easily and significantly influence CAR estimates (e.g., timing and dynamic of the peak) [70].

While all studies report shiftwork significantly influences waking levels of cortisol (i.e., the first sample sychronised with the moment of awakening) and the dynamic of post-awakening cortisol secretion, reported as either CAR_i (identifies changes in the CAR overtime but is sensitive to the first awakening sample) or area under the curve in relation to ground (AUCg) mixed findings have again emerged.

Though waking cortisol samples were obtained in all studies, not all papers reported an outcome for this measure. Waking levels are considered the starting point of the CAR period [70]. Four studies [66, 68–70][69, 71–73] found waking levels to be significantly higher in day shiftworkers compared to night shift and afternoon shiftworkers. In contrast, Bostock et al. [74] and Federenko et al. [75] found individuals waking prior to 0530h displayed lower waking levels. Additionally, one week off roster, after working 14 consecutive night shifts individuals displayed significantly lower waking levels of cortisol compared to their baseline [67]. Further, Lammers-van der Holst [76] found the mean increase values (MnInc: based on the average of all post awakening samples) of post awakening cortisol secreted across the CAR period (i.e., samples at 15min or 30 min intervals in the first hour post awakening) in individuals transitioning from regular day work hours to a rotating shift schedule was significantly higher between four and 14-months after transitioning compared to baseline levels. For some participants these levels reverted to a smaller baseline level cortisol response at ~20 months after commencing a shiftwork schedule. Authors suggested this reversal to baseline may be indicative of a process of recovery or development of a tolerance to shiftwork.

CAR itself was reported to be higher on workdays in day shift and irregular shiftworkers compared to their days off [69]. CAR is evident in night shiftworkers (sleeping during the day) but was found to be significantly smaller compared with day shiftworkers [66, 77] while CAR was most pronounced when awakening occurred very early in the morning (e.g., 0400h) for individuals working an early shift [75]. Additionally, after the first night of night shift on a 14-day night shift roster CAR was significantly lower, but on the last night of night shift (night 14) there were no differences in CAR compared to individuals

working day shift. In contrast, on the last day of a swing shift (Table 2) CAR was low compared to day shiftworkers [49]. For individuals working 'on-call' and responding to call-outs, CAR peak the following morning was attenuated with lower post awakening cortisol levels [68]. In contrast to this Dettenborn et al. [78] reported CAR across the night and the morning after following a night of interrupted sleep (three 15-minute awakenings across the night). No differences were seen in CAR following each awakening and CAR the following morning did not differ from CAR on the morning following a night of undisturbed sleep. Notably, only two saliva samples were collected on each night awakening and the following morning, that is immediately on awakening and 15-minutes post awakening. The impact of these awakenings may have been more evident had additional samples been collected over the full CAR period (30,45 and 60-minutes post awakening). Furthermore, working long term night shift is associated with an attenuated CAR but not significantly [72, 73].

CAR_i, was found to be significantly lower in afternoon and night shiftworkers compared to day shiftworkers [69, 71] while early shiftworkers (i.e., waking before 0530h) displayed higher CAR_i compared with night shiftworkers and workers on their day off [74, 75]. Night shift, afternoon shift, and 'on-call' workers who respond to call-outs during the night additionally display significantly lower mean values for total cortisol output over the entire CAR period (AUC_g), compared with day shiftworkers [68, 72, 73, 79]. Individuals working five consecutive night shifts, by days three and four, displayed significantly flatter waking to +30 minutes (i.e., CAR_i) compared to day shiftworkers [42].

The literature regarding CAR and shiftwork induced disruptions is very limited. Waking levels appear to reflect 'normal' diurnal levels, that is, individuals waking prior to 0500h, late morning or mid to late-afternoon all display low levels which coincide with the

diurnal levels of cortisol at these times. However, CAR and its associated measurements (CAR_i and AUC_g) all display a significant degree of attenuation in late evening and night shiftworkers but not in individuals waking extremely early (e.g., 0400). Additionally, data collection methodology (i.e., the number, timing of samples and number of consecutive days) should be carefully considered when interpreting data. Non-compliance with sampling time instructions has been linked with results in false estimates of high waking levels and low estimates of CAR. Additionally, collection of only two post-awakening samples cannot accurately capture CAR [70].

Discussion

This scoping review provided an overview of the shiftwork induced disruptions to cortisol. The findings demonstrate that 1) shiftwork, especially night shift induces significant disruptions to cortisol production, the cortisol rhythm and CAR; such that a) levels at night are high when they would normally be low, b) levels remain higher across the day the more consecutive night shifts individuals work, c) the cortisol slope flattens over consecutive night shifts and d) the dynamic of CAR is attenuated, 2) irregular shift schedules may produce greater disruptions to cortisol than regular shift schedules, 3) data on the acute and on-going effects of sleep restriction on cortisol in shiftworkers is lacking and 4) there is conflicting data and no consistency in the choice of a reliable outcome measure or number of days on shift/off shift used to conclude adaptation and or recovery of the cortisol rhythm to and from night shift.

Findings of this review demonstrate that shiftwork, especially night shift significantly disrupts the production of cortisol. When this is chronic, it can induce allostatic overload [31], predisposing individuals to poor health [30]. Importantly, of the 37 studies reviewed, 24

investigated the effect of shiftwork on cortisol over one or two-days. This scoping review indicates that more longitudinal research is needed, investigating the cumulative effects of repetitive disruption to cortisol secretion in shiftworkers. Evidence from the reviewed studies suggests that irregular shift schedules, that is, rotating from one shift type to another over several days, may produce sustained changes in cortisol secretion due to circadian dysregulation which may, in the long run, result in chronic long term maladaptive cortisol levels. Research should explore whether repeated disruptions to cortisol may be a physiological mediator for increased chronic health risks in shiftworkers such as cardiovascular disease and metabolic syndrome which additionally increases the risk for type II diabetes [32, 80, 81]. In addition to sleep disruption, restriction, and circadian misalignment, shiftwork results in altered meal timing. [1, 2, 80]. This scoping review revealed limited research exploring behaviours like meal timing and cortisol levels in shiftworkers. Such behavioural changes likely, to some extent, explain or exacerbate shiftwork-related alterations to physiological systems that underlie glucose tolerance, insulin sensitivity and alteration in inflammatory markers. All these systems are influenced or regulated by cortisol [82–84] and increased circulating levels of cortisol, similar to that reported in some of the reviewed studies, may contribute to disease development [81, 85, 86]. There is urgent need for research to better understand the relationship between sleep restriction, meal timing, cortisol levels and associated alterations to physiological systems which are regulated by cortisol. Such research would be foundational for developing interventions for improved health in shiftworkers.

The reviewed literature on shiftwork and the adaptation and recovery of the cortisol rhythm to night shifts is limited to a small number of papers with variation in methods, schedules and interpretation of when or if the cortisol rhythm adapts to and or recovers from consecutive

night shifts, making comparison difficult. To better understand and accurately identify these shiftwork induced phenomena it is suggested that as a field, clearer and more consistent definitions of reversal, adaptation, or recovery of the cortisol rhythm would be of great benefit.

The majority of reviewed studies focuses on the disruption in health professionals and protective service workers which are naturally stressful vocations. Of the 37 studies reviewed only one study examined changes in cortisol as a function of different job roles on a night shift. The cortisol levels of security guards inspecting properties at night increased significantly before and after their night shift compared to security guards based in a monitoring room [45]. The work environment, the job role and their related stressors are likely to trigger the HPA axis influencing the release of cortisol [87]. Evidence suggests the impact of stress, either psychological and or physical may be additive to the circadian changes associated with shiftwork [45, 57, 88]. It would be useful to disentangle stress and circadian disruption. Therefore, it is recommended that future research take this into consideration and investigate vocations with varying stress profiles, possibly assessing shiftworkers during vacation time vs. work time/duties, to provide a more comprehensive understanding of the degree of disruption to cortisol. Such research may steer the development of different targeted interventions to shiftworker health.

In conclusion, shiftwork, especially night shift induces significant disruptions to the production of cortisol, the cortisol rhythm, and CAR. There is evidence that shiftwork disrupts the production of cortisol and that the level of disruption varies according to shift type, irregular schedules, and sleep restriction. The implications of long-term recurring and cumulative disruptions are not well-understood. The significance of these changes must be established by more longitudinal research. Observing such changes will help to develop a

comprehensive knowledge of the impact of repeated system disruptions in shiftworkers, and establish the role of cortisol in future health risks

Practice points

1. Irregular shift schedules rather than the shift type itself may influence the observed changes in the cortisol rhythm.
2. There is need for clearer and more consistent means to accurately identify reversal, adaptation and recovery of the cortisol rhythm.
3. A more comprehensive understanding of the degree of disruption to cortisol in vocations with varying stress profiles is needed.

Research agenda

1. Further research is need to better understand the relationship between sleep restriction, meal timing, cortisol levels and associated alterations to physiological systems regulated by cortisol.
2. Research demonstrates the acute impact of shiftwork-induced disruption to cortisol, but longitudinal research is needed, to investigate the cumulative effects of repetitive disruption to cortisol secretion in shiftworkers.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

References

[1] Haus E, Smolensky M. Biological Clocks and Shift Work: Circadian Dysregulation and Potential Long-Term Effects. *Cancer Causes Control* 2006; 17: 489–500.

[2] Herichova I. Changes of physiological functions induced by shift work. *Endocr Regul* 2013; 47: 159–70.

[3] James SM, Honn KA, Gaddameedhi S, et al. Shift Work: Disrupted Circadian Rhythms and Sleep—Implications for Health and Well-being. *Curr Sleep Med Rep* 2017; 3: 104–112.

[4] Costa G. Factors influencing health of workers and tolerance to shift work. *Theor Issues Ergon Sci* 2003; 4: 263–288.

[5] Lac G, Chamoux A. Biological and psychological responses to two rapid shiftwork schedules. *Ergonomics* 2004; 47: 1339–1349.

[6] Koch CE, Leinweber B, Drengberg BC, et al. Interaction between circadian rhythms and stress. *Neurobiol Stress* 2016; 6: 57–67.

[7] Tsigos C, Chrousos GP. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *J Psychosom Res* 2002; 53: 865–871.

*[8] Clow A, Hucklebridge F, Thorn L. The cortisol awakening response in context. In: *International review of neurobiology*. Elsevier, 2010, pp. 153–175.

[9] Heaney J. Hypothalamic-Pituitary-Adrenal Axis. In: Gellman MD, Turner JR (eds) *Encyclopedia of Behavioral Medicine*. New York, NY: Springer New York, pp. 1017–1018.

[10] Liyanarachchi K, Ross R, Debono M. Human studies on hypothalamo-pituitary-adrenal (HPA) axis. *Best Pract Res Clin Endocrinol Metab* 2017; 31: 459–473.

[11] Born J, Kern W, Bieber K, et al. Night-time plasma cortisol secretion is associated with specific sleep stages. *Biol Psychiatry* 1986; 21: 1415–1424.

[12] Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology* 2009; 34: 163–171.

[13] Selmaoui B, Touitou Y. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects: a study of three different 24-h cycles over six weeks. *Life Sci* 2003; 73: 3339–3349.

[14] Stone AA, Schwartz JE, Smyth J, et al. Individual differences in the diurnal cycle of salivary free cortisol: a replication of flattened cycles for some individuals. *Psychoneuroendocrinology* 2001; 26: 295–306.

*[15] Clow A, Thorn L, Evans P, et al. The Awakening Cortisol Response: Methodological Issues and Significance. *Stress* 2004; 7: 29–37.

[16] Pruessner JC, Wolf OT, Hellhammer DH, et al. Free cortisol levels after awakening: a reliabile biological marker for the assessment of adrenocortical activity. 1997; 61: 11.

[17] Pruessner JC, Hellhammer DH, Kirschbaum C. *perceived stress, and cortisol response to awakening. Psychosom Med*. 1999.

[18] Wilhelm I, Born J, Kudielka BM, et al. Is the cortisol awakening rise a response to awakening? *Psychoneuroendocrinology* 2007; 32: 358–366.

[19] Clow A, Hucklebridge F, Stalder T, et al. The cortisol awakening response: More than a measure of HPA axis function. *Neurosci Biobehav Rev* 2010; 35: 97–103.

[20] Huber TJ, Issa K, Schik G, et al. The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. *Psychoneuroendocrinology* 2006; 31: 900–904.

[21] Wessa M, Rohleder N, Kirschbaum C, et al. Altered cortisol awakening response in posttraumatic stress disorder. *Psychoneuroendocrinology* 2006; 31: 209–215.

[22] Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): Facts and future directions. *Int J Psychophysiol* 2009; 72: 67–73.

[23] Steptoe A, Serwinski B. Cortisol Awakening Response. In: *Stress: Concepts, Cognition, Emotion, and Behavior*. Elsevier, pp. 277–283.

[24] Hucklebridge FH, Clow A, Abeyguneratne T, et al. The awakening cortisol response and blood glucose levels. *Life Sci* 1999; 64: 931–937.

[25] Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. *Trends Pharmacol Sci* 2013; 34: 518–530.

[26] Spencer RL, Deak T. A users guide to HPA axis research. *Physiol Behav* 2017; 178: 43–65.

[27] Buckingham JC. Glucocorticoids: exemplars of multi-tasking. *Br J Pharmacol* 2006; 147: S258–S268.

[28] Chung S, Son GH, Kim K. Circadian rhythm of adrenal glucocorticoid: Its regulation and clinical implications. *Biochim Biophys Acta BBA - Mol Basis Dis* 2011; 1812: 581–591.

[29] Munck A, Náray-Fejes-Tóth A. The ups and downs of glucocorticoid physiology Permissive and suppressive effects revisited. *Mol Cell Endocrinol* 1992; 90: C1–C4.

[30] McEwen BS. Stressed or stressed out: What is the difference? *J Psychiatry Neurosci* 2005; 30: 315–318.

[31] McEwen BS, Karatsoreos IN. Sleep Deprivation and Circadian Disruption. *Sleep Med Clin* 2015; 10: 1–10.

[32] Puttonen S, Härmä M, Hublin C. Shift work and cardiovascular disease — pathways from circadian stress to morbidity. *Scand J Work Environ Health* 2010; 36: 96–108.

[33] Ritonja J, Aronson KJ, Day AG, et al. Investigating Cortisol Production and Pattern as Mediators in the Relationship Between Shift Work and Cardiometabolic Risk. *Can J Cardiol* 2018; 34: 683–689.

[34] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *The lancet* 1999; 354: 1435–1439.

[35] Costa G, Di Milia L. Aging and Shift Work: A Complex Problem to Face. *Chronobiol Int* 2008; 25: 165–181.

[36] Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005; 8: 19–32.

[37] Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010; 5: 69.

[38] Leproult R, Colecchia EF, Riaux ML-B, et al. Transition from Dim to Bright Light in the Morning Induces an Immediate Elevation of Cortisol Levels. 2001; 86: 7.

[39] Pruessner JC, Hellhammer DH, Kirschbaum C. Burnout, perceived stress, and cortisol responses to awakening. *Psychosom Med* 1999; 61: 197–204.

[40] Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. *Psychoneuroendocrinology* 1994; 19: 313–333.

[41] Peters M, Godfrey C, McInerney P, et al. Chapter 11: Scoping Reviews (2020 version). In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis, JBI, 2020. In: *JBI Manual For Evidence Synthesis: Chapter 11: Scoping Reviews (2020 version).*, https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-12 (2020).

*[42] Niu S-F, Chung M-H, Chu H, et al. Differences in cortisol profiles and circadian adjustment time between nurses working night shifts and regular day shifts: A prospective longitudinal study. *Int J Nurs Stud* 2015; 52: 1193–1201.

[43] Anjum B, Verma NS, Tiwari S, et al. Association of salivary cortisol with chronomics of 24 hours ambulatory blood pressure/heart rate among night shift workers. *Biosci Trends* 2011; 7.

[44] Touitou Y, Motohashi Y, Reinberg A, et al. Effect of shift work on the night-time secretory patterns of melatonin, prolactin, cortisol and testosterone. *Eur J Appl Physiol* 1990; 60: 288–292.

[45] Cannizzaro E, Cirrincione L, Mazzucco W, et al. Night-Time Shift Work and Related Stress Responses: A Study on Security Guards. *Int J Environ Res Public Health* 2020; 17: 562.

[46] Carev M, Karanovi N, Bagatin J, et al. Blood Pressure Dipping and Salivary Cortisol as Markers of Fatigue and Sleep Deprivation in Staff Anesthesiologists. *Coll Antropol* 2011; 6.

[47] Choshen-Hillel S, Ishqer A, Mahameed F, et al. Acute and chronic sleep deprivation in residents: Cognition and stress biomarkers. *Med Educ* 2021; 55: 174–184.

[48] Ernst F, Rauchenzauner M, Zoller H, et al. Effects of 24h working on-call on psychoneuroendocrine and oculomotor function: A randomized cross-over trial. *Psychoneuroendocrinology* 2014; 47: 221–231.

*[49] Harris, Waage S, Ursin H, et al. Cortisol, reaction time test and health among offshore shift workers. *Psychoneuroendocrinology* 2010; 35: 1339–1347.

[50] Jensen MA, Hansen ÅM, Kristiansen J, et al. Changes in the diurnal rhythms of cortisol, melatonin, and testosterone after 2, 4, and 7 consecutive night shifts in male police officers. *Chronobiol Int* 2016; 33: 1280–1292.

[51] Fujiwara S, Shinkai S, Kurokawa Y, et al. The acute effects of experimental short-term evening and night shifts on human circadian rhythm: the oral temperature, heart rate, serum cortisol and urinary catecholamines levels. *Int Arch Occup Environ Health* 1992; 63: 409–418.

[52] Thomas C, Hertzman C, Power C. Night work, long working hours, psychosocial work stress and cortisol secretion in mid-life: evidence from a British birth cohort. *Occup Environ Med* 2009; 66: 824–831.

[53] Morales J, Yáñez A, Fernández-González L, et al. Stress and autonomic response to sleep deprivation in medical residents: A comparative cross-sectional study. *PLOS ONE* 2019; 14: e0214858.

[54] Hall SJ, Aisbett B, Tait JL, et al. The acute physiological stress response to an emergency alarm and mobilization during the day and at night. *Noise Health* 2016; 18: 150.

*[55] Vangelova K. The Effect of Shift Rotation on Variations of Cortisol, Fatigue and Sleep in Sound Engineers. *Ind Health* 2008; 46: 490–493.

[56] Korompeli A, Sourtzi P, Tzavara C, et al. Rotating shift-related changes in hormone levels in intensive care unit nurses. *J Adv Nurs* 2009; 65: 1274–1282.

*[57] Wolkow A., Aisbett B., Reynolds J., et al. The impact of sleep restriction while performing simulated physical firefighting work on cortisol and heart rate responses. *Int Arch Occup Environ Health* 2016; 89: 461–475.

[58] Guyon A, Balbo M, Morselli LL, et al. Adverse Effects of Two Nights of Sleep Restriction on the Hypothalamic-Pituitary-Adrenal Axis in Healthy Men. *J Clin Endocrinol Metab* 2014; 99: 2861–2868.

[59] Charles LE, Fekedulegn D, Burchfiel CM, et al. Shiftwork and Diurnal Salivary Cortisol Patterns Among Police Officers. *J Occup Environ Med Am Coll Occup Environ Med* 2016; 58: 542–549.

[60] Hennig J, Kieferdorf P, Moritz C, et al. Changes in cortisol secretion during shiftwork: implications for tolerance to shiftwork? *Ergonomics* 1998; 41: 610–621.

[61] Weibel L, Spiegel K, Follenius M, et al. Internal dissociation of the circadian markers of the cortisol rhythm in night workers. *Am J Physiol-Endocrinol Metab* 1996; 270: E608–E613.

[62] Roden M, Koller M, Pirich K, et al. The circadian melatonin and cortisol secretion pattern in permanent night shift workers. *Am J Physiol-Regul Integr Comp Physiol* 1993; 265: R261–R267.

[63] Li J, Bidlingmaier M, Petru R, et al. Impact of shift work on the diurnal cortisol rhythm: a one-year longitudinal study in junior physicians. *J Occup Med Toxicol* 2018; 13: 1–9.

[64] Karlson B, Carlsson Eek F, Hansen AM, et al. Diurnal cortisol pattern of shift workers on a workday and a day off. *Scand J Work Environ Health* 2006; 32: 27.

[65] Motohashi Y. Alteration of circadian rhythm in shift-working ambulance personnel. Monitoring of salivary Cortisol rhythm. *Ergonomics* 1992; 35: 1331–1340.

[66] Kudielka BM, Buchtal J, Uhde A, et al. Circadian cortisol profiles and psychological self-reports in shift workers with and without recent change in the shift rotation system. *Biol Psychol* 2007; 74: 92–103.

[67] Merkus SL, Holte KA, Huysmans MA, et al. Neuroendocrine recovery after 2-week 12-h day and night shifts: an 11-day follow-up. *Int Arch Occup Environ Health* 2015; 88: 247–257.

[68] Hall SJ, Turner AI, Robertson SJ, et al. Salivary cortisol profiles of on-call from home fire and emergency service personnel. *Stress* 2019; 22: 436–445.

[69] Ulhôa MA, Marqueze EC, Kantermann T, et al. When Does Stress End? Evidence of a Prolonged Stress Reaction in Shiftworking Truck Drivers. *Chronobiol Int* 2011; 28: 810–818.

*[70] Stalder T, Kirschbaum C, Kudielka BM, et al. Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrinology* 2016; 63: 414–432.

*[71] Chang W-P. Influence of shift type on sleep quality of female nurses working monthly rotating shifts with cortisol awakening response as mediating variable. *Chronobiol Int* 2018; 35: 1503–1512.

[72] Fekedulegn D, Burchfiel CM, Violanti JM, et al. Associations of Long-term Shift Work with Waking Salivary Cortisol Concentration and Patterns among Police Officers. *Ind Health* 2012; 50: 476–486.

[73] Wirth M, Burch J, Violanti J, et al. Shiftwork Duration and the Awakening Cortisol Response Among Police Officers. *Chronobiol Int* 2011; 28: 446–457.

[74] Bostock S, Steptoe A. Influences of early shift work on the diurnal cortisol rhythm, mood and sleep: Within-subject variation in male airline pilots. *Psychoneuroendocrinology* 2013; 38: 533–541.

[75] Federenko I, Wüst S, Hellhammer DH, et al. Free cortisol awakening responses are influenced by awakening time. *Psychoneuroendocrinology* 2004; 29: 174–184.

[76] Lammers-van der Holst HM, Kerkhof GA. Individual differences in the cortisol-awakening response during the first two years of shift work: A longitudinal study in novice police officers. *Chronobiol Int* 2015; 32: 1162–1167.

[77] Griefahn B, Robens S. The cortisol awakening response: A pilot study on the effects of shift work, morningness and sleep duration. *Psychoneuroendocrinology* 2008; 33: 981–988.

[78] Dettenborn L, Rosenloecher F, Kirschbaum C. No effects of repeated forced wakings during three consecutive nights on morning cortisol awakening responses (CAR): A preliminary study. *Psychoneuroendocrinology* 2007; 32: 915–921.

[79] Vincent GE, Jay SM, Preece H, et al. Overnight heart rate variability and next day cortisol response during simulated on-call conditions. *Psychoneuroendocrinology* 2019; 109: 104406.

[80] Knutsson A. Health disorders of shift workers. *Occup Med* 2003; 53: 103–108.

[81] Anagnostis P, Athyros VG, Tziomalos K, et al. The Pathogenetic Role of Cortisol in the Metabolic Syndrome: A Hypothesis. *J Clin Endocrinol Metab* 2009; 10.

[82] Casement MD, Broussard JL, Mullington JM, et al. The contribution of sleep to improvements in working memory scanning speed: A study of prolonged sleep restriction. *Biol Psychol* 2006; 72: 208–212.

[83] Knutson KL, Spiegel K, Penev P, et al. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007; 11: 163–178.

[84] Leproult R, Van Cauter E. Role of Sleep and Sleep Loss in Hormonal Release and Metabolism. In: Loche S, Cappa M, Ghizzoni L, et al. (eds) *Endocrine Development*. Basel: KARGER, pp. 11–21.

*[85] Rogers M, Coates AM, Banks S. Meal timing, Sleep and Cardiometabolic Outcomes. *Curr Opin Endocr Metab Res*.

[86] Manenschijn L, Schaap L, van Schoor NM, et al. High Long-Term Cortisol Levels, Measured in Scalp Hair, Are Associated With a History of Cardiovascular Disease. *J Clin Endocrinol Metab* 2013; 98: 2078–2083.

[87] Lundberg U. Coping with stress: neuroendocrine reactions and implications for health. *Noise Health* 1999; 1: 67–74.

[88] Cannizzaro E, Plescia F, Cirrincione L, et al. Sport for job. differences in cortisol levels in a water polo team at different times of workout. *Euromediterranean Biomed J* 2018; 13: 181–184.