Does night work affect age at which menopause occurs?

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Purpose of review
To delineate the current state of evidence on the impact of night shift work on age at natural menopause.

Recent findings
The only direct evidence is from a single observational study, which indicates that women who work night shifts are at moderately higher risk for earlier menopause and that this risk is more pronounced among younger women. Underlying biological mechanisms have yet to be sufficiently substantiated. A long-held line of inquiry, most strongly propagated by the observed link between night shift work and female breast cancer, is the 'Light at Night' hypothesis, which suggests melatonin-mediated circadian disruption as a potential regulator of reproductive signaling in women. Supporting evidence is found from observations of changes in endogenous melatonin production among night working women or in response to light exposure, and corresponding changes in endogenous ovarian hormone levels and modulated menstrual patterns, among other indications of altered central ovulation-governing processes. Susceptibility to night shift work may be modified by chronotype.

Summary
This review summarizes the literature related to night work and ovulatory regulation in humans, prioritizing population-based evidence to provide motivation for the study of circadian disruption and night shift work as a regulator of menopausal timing.

Keywords
chronotype, circadian disruption, menopausal age, night shift work, ovulation

INTRODUCTION: MENOPAUSE AS A MARKER OF DISEASE RISK

Menopause and the age at which it occurs have been identified as markers of chronic disease and adverse health outcomes (e.g. rheumatoid arthritis, depression). Of the most prominent adverse outcomes associated with older age of menopause are cancers, particularly those of reproductive organs, including endometrial [1], ovarian [2] and breast cancer. For the latter, a meta-analysis combining 117 observational studies including 118 964 women with invasive breast cancer and 425 055 women in total, reported a pooled, statistically significant 3% (95% confidence interval (CI) 2.6–3.4%) increased risk with each year older at menopause [3]. Conversely, earlier menopause has been linked with cognitive decline, osteoporosis, colorectal cancer, coronary heart disease, diabetes and lower life expectancy. However, the underlying mechanisms linking menopausal timing to disease risk are not well established.

A long-studied prevailing theory linking menopausal timing to health outcomes features exposure to endogenous sex hormones, particularly ovarian estrogen, which declines precipitously during the menopausal transition. Premature reduction in these hormones has been linked to cardiovascular disease [4] and reduced bone density [5]. Earlier menopause and timing of attenuation of endogenous estrogens may increase risk of cognitive decline and dementias. A growing awareness of a negative impact of the suppression of estrogen signaling on cognitive function has been recognized among women on long-term estrogen-blocking

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KEY POINTS

- Menopausal age has been observed as a risk factor for adverse health outcomes: younger age at menopause has been associated with age-related conditions, such as frailty, diabetes and cognitive decline; older age at menopause with reproductive cancers.
- Night shift work has also been associated with poorer health, the most studied of which has been female breast cancer, and may exert regulatory control over ovulation.
- Though biological mechanisms by which night shift work impacts menopausal timing, and more generally ovulation, in humans is unknown, a prevailing theory involves melatonin-mediated circadian disruption attributed mainly to exposure to bright light during normatively dark periods (i.e. light at night).
- There has only been a single published observational study specifically on the association between night shift work and age at natural menopause, which found that women who worked recent and lifelong rotating night shifts, particularly those under 45 years, were at moderate risk of earlier menopause.
- Although there is insufficient evidence to restrict women from working night shifts, further investigation should focus on women of specific chronotype (i.e. morning preference) or otherwise already at higher risk of earlier menopause.

adjuvant therapies for estrogen-receptor positive cancers [6]. Though inconclusive, estrogens have been observed to inhibit key neurological precursors of Alzheimer's disease [7–10] and have exhibited protective potential against neurological damage associated with trauma [11] or ischemic events [12] through attenuation of oxidative stress, inflammation and promotion of vascular health [11]. Conversely, increased cumulative exposure to circulating reproductive hormones associated with later menopause is thought to be a main driver of increased reproductive cancer risk.

DRIVERS OF THE MENOPAUSAL TRANSITION

Natural menopause has been viewed as a marker of biological aging, with earlier natural menopause being associated with lower life expectancy and age-linked conditions, such as cardiovascular disease [13] or musculoskeletal frailty [14]. Findings suggesting age at natural menopause to be linked to telomere length [15] or genetic variation in DNA-repair enzymes [16] may provide some corroboration.

In the United States, the average age of menopause is 51 years, ranging between 48 and 52 years across industrialized countries [17]. Natural menopause occurs when there is an insufficient number of primordial follicles in ovarian reserve to induce progression to primary follicles, preventing ovulation. The timing of this threshold, marking the end of a women's natural reproductive lifetime, is dependent upon ovarian supply produced during fetal development and rate of follicle atresia thereafter [17,18]. Primordial follicle progression is governed by endocrine feedback between the follicles and gonadotropic neurons of the pituitary and hypothalamus, though this regulatory mechanism has not been fully elucidated in humans [19]. There is a strong genetic component to the age at which natural menopause is achieved, with multiple candidate genes and genomic loci identified [20–22], the number of which are growing [16]. Familial studies estimating variation in age at natural menopause attributable to heritable factors [23–26] have been variable, though most estimates range between 40 and 50% [23,24,27], leaving room for environmental causes. Several modifiable risk factors have been linked to age at natural menopause, such as diet, physical activity, adiposity, oral contraceptive use, lower parity, socioeconomic status, and smoking-related exposures [28–31]. Smoking, particularly being a current smoker with a history of high intensity cumulative use [32,33], has been most strongly and reliably associated with early natural menopause. Although a substantial proportion of unexplained variability remains, the apparent regulatory complexity of ovulation by targets across the hypothalamic–pituitary–ovarian axis (HPOA) renders identification of candidates challenging.

NIGHT SHIFT WORK AND WOMENS' REPRODUCTIVE HEALTH: A BRIEF HISTORY

Over the latter half of the 20th century, female workforce participation in countries such as the United States rose considerably, and with it, the relevancy of occupational risk factors for women's health, such as night shift work (NSW). Today, the potential for NSW to negatively impact womens' health is becoming difficult to deny. Although there are no randomized controlled trials directly linking shift work to increased disease risk, the observational evidence continues to mount. Night-working women are potentially at greater risk of chronic conditions including cardiovascular disease [34,35], metabolic syndrome [36–38], obesity and type 2 diabetes [39–42]. Further, NSW has been associated with adverse reproductive outcomes including preterm delivery [43] and miscarriage

[44], modification of menstrual cycle patterns [45–47] and increased risk of certain cancers. Night shift work was recognized as a 'probable carcinogen' by the International Agency for Research on Cancer in 2007, and reconfirmed as such by the working group in a 2019 update [48▪]. The 2007 declaration was based on 'limited evidence in humans for the carcinogenicity of shift-work that involves night work', which has since been increasing, and 'sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period' [49]. Among humans, the preponderance of the evidence for the carcinogenicity of NSW has been from observational studies of female breast cancer, with more recent evidence from prostate and colorectal sites [48▪].

The early focus of these studies on breast cancer stemmed primarily from the 'light at night (LAN) hypothesis', which accredited rising rates in developed countries, particularly in metropolitan areas, to the growing ubiquitousness of nocturnal electric light-induced circadian disruption [50]. Due to the recognition that night work involved exposure to LAN, initial challenges involved in measuring LAN or related biomarkers reliably in large samples led NSW to become a popular surrogate exposure for LAN-induced circadian disruption. Observations from rodent models that such exposures suppress nocturnal pineal melatonin secretion, and that lower melatonin or pinealectomy was in turn correlated with reduced resistance to chemically induced mammary tumourigenesis, singled the hormone out as a key endocrine mediator. Demonstration that melatonin supplementation coincided with decreased circulating estradiol and prolactin [51] suggested a tumorigenic pathway featuring amplification of reproductive endocrine signaling involved in ovulatory control. The implication that nocturnal melatonin suppression because of LAN may upregulate HPOA activity leading to elevated circulating sex hormones suggested a regulatory effect on timing of menopausal onset, which is marked by a striking reduction in endogenous production of these hormones.

The LAN hypothesis coincided with a growing recognition of the oncogenic potential of sex hormones and a prevailing theory was that women exposed to higher levels of sex steroids, particularly estrogens, over their reproductive lifetime would be at greater risk for breast and other reproductive cancers [52]. Studies in humans have supported a suppressive, phase-shifting effect of LAN on peak nocturnal pineal melatonin production [53,54,55▪]. An inverse relationship between endogenous melatonin and ovarian estradiol has been reported [56,57]. Larger epidemiological studies, however, have been mostly null [58–60], though one study found higher levels of estradiol among rotating night workers starting a morning shift following a day off, compared with exclusively day workers [61].

IS OVULATION UNDER MELATONIN-MEDIATED CIRCADIAN REGULATION?

Mechanisms of melatonin-mediated photoperiodic (i.e. natural daylight length) control of gonadal function has been delineated in seasonally breeding mammals for more than half a century [62]. Although humans are not seasonal breeders, conception rates have historically varied both by latitude and season, not all of which are likely explained by social cues [63]. Seasons of longer photoperiod (e.g. spring), and corresponding lower pineal nocturnal melatonin production, have been correlated with markers of enhanced HPOA activity including relatively elevated gonadotropin and estradiol production [64–66]. Though these findings were among nonrandomized, small samples of women, if valid, are suggestive of a circadian regulatory effect on ovulation shared with other mammals. Despite a general failure to characterize causal relationships between endogenous melatonin and sex hormones, as outlined earlier, morning levels of melatonin were shown to be inversely correlated with estradiol in luteal and follicular phases of 20 women aged 25–30 years [56].

Morning melatonin supplementation, temporally distal from the typical peak nocturnal endogenous signal, has been observed to enhance gonadotropin release during the follicular phase in some studies [67,68], potentially promoting follicle progression, questioning its suppressive effect on gonadal activity. Other intervention studies have observed associations between long-term supplementation and circulating reproductive hormones, but these have been limited largely to postmenopausal women [69–72] and overall, results have been mixed.

Although this may appear to be at odds with the LAN hypothesis characterizing melatonin as an inhibitor of HPOA activation, and thereby ovulation, it might be speculated that daytime supplementation is disruptive of the endogenous nocturnal melatonin signal, perhaps having an opposing effect on gonadotropins; regulation of these hormones by melatonin may depend on time of day. Support for this is found in the investigation of melatonin supplementation on phase advances and delays of the natural nocturnal melatonin signal [73]. Nocturnal secretion was advanced most profoundly by afternoon melatonin supplementation and delayed by exogenous melatonin taken in the morning. Though speculative in humans,

diurnal variation in melatonin receptor density at central sites, as observed in rodent models [74], could explain opposing effects of spikes in circulating melatonin at opposite times of the day. Furthermore, long-term daily high-dose supplementation, perhaps sufficient to override the endogenous signal rather than merely phase shift it, has been reported to reduce circulating luteinizing hormone and estradiol levels in cycling women and could be because of inhibition of the HPOA axis [75].

Though pineal melatonin is an established regulator of gonadal activity in some mammals, how it impacts the HPOA to exert this control remains incompletely understood. Models have been proposed linking the receptor-mediated nocturnal melatonin signal in the pars tuberalis to gonadotropic control via the gonadotropin-releasing hormone (GnRH) pulse from the median eminence [76,77]. Though none have been robustly demonstrated *in vivo*, melatonin has been observed to suppress GnRH gene expression *in vitro* through MT1-recpetor mediated signal transduction [78]. Pineal melatonin acts broadly as a conveyor of circadian cues by triggering, or regulating the periodicity of, gene expression at many central and peripheral targets [79]. The discovery of melatonin signal-driven gene expression in the mammalian hypothalamus could be suggestive of undiscovered pathways by which the hormone may affect central gonadotropic control [80,81]. Further, the regulation of the GnRH signal is multifactorial, as it receives input from afferent neurons, steroid hormone feedback, and a growing number of identified neuromodulators [82,83].

Experimental studies have reported melatonin to vary negligibly over the menstrual cycle in healthy women [84–89], though conflicting findings exist [56,90–92]. Heterogeneity stemming from small samples, variation in melatonin measurement, and potential differences in participant characteristics pose challenges to drawing firm conclusions. A relatively stable endogenous melatonin rhythm over the menstrual cycle supports the idea that regulation of gonadal activity because of changes in nocturnal melatonin levels requires long-term entrainment. Inverse correlations between luteinizing hormone [65] and estradiol [64] during ovulatory [64,65] and luteal phases [64], corresponding to seasonal fluctuations in melatonin levels, have been observed. This may explain the lack of corresponding changes in circulating reproductive hormones in response to acute melatonin suppression because of LAN or between endogenous melatonin and circulating ovarian hormones previously discussed. Direct evidence for a delayed effect of melatonin on gonadal activity comes from experimental findings reporting shortened menstrual cycle lengths in women exposed to LAN for multiple consecutive days [93–95].

Finally, melatonin may promote ovulation and delay menopause by protecting follicle integrity at the ovary directly [96,97]. In summary, although there are indications that at least some of the mechanisms of melatonin-mediated circadian regulation of gonadal activity observed in other mammals are conserved in humans, there has been insufficient evidence to definitively characterize functional impact of the hormone on ovulation in women.

NIGHT SHIFT WORK AND MENOPAUSE

Irrespective of the role of melatonin, circadian regulation of ovulatory processes is supported by findings that LAN can shorten menstrual cycles [93] and of shorter menstrual cycles among night workers [45–47]. These findings are, in turn, compatible with the association between NSW and earlier age at menopause observed in the Nurses' Health Study (NHS) 2 cohort [98▪▪]. Among nurses under 45 years, there was a 25% increased risk of self-reported menopause for those having worked 20 or more months of rotating night shifts (i.e. months in which at least 3 nights, in addition to day and evening shifts, were worked) in the previous 2 years compared with those who did not work these schedules. This increased risk was conserved for all ages, though was attenuated to approximately 10% in the overall cohort. Relative to women who never worked rotating night shift schedules, cumulative lifelong exposure of 20 or more years (i.e. summed months in which at least 3 nights, in addition to day and evening, shifts were worked) was similarly associated with earlier menopause, and again, the effect was stronger among women under the age of 45 years.

It is difficult to explain the relatively elevated risk of menopause because of night work for younger women (i.e. <45 years). If real, one possibility may be variation in innate tolerance. Women reported less night work with age in the NHS2 [98▪▪]. It could be that older women not yet menopausal, perhaps allotted more autonomy over their work schedule because of occupational seniority than their younger counterparts, were more likely to self-select against night work if less biologically tolerant. Supporting evidence comes from observations that the degree to which endogenous melatonin production is compromised by night work and LAN exposure varies by chronotype (i.e. alertness in the morning versus at night). Recent epidemiological studies examining the relationship between LAN, makers of circadian disruption and chronotype have been mixed [55▪,61,99–101], possibly partly because of methodological variation in the

assessment of chronotype and heterogeneity across study samples. Results from a subsample of the NHS2 cohort suggest that those with morning chronotypes may be less tolerant to night work, and by extension, more susceptible to related adverse health outcomes, such as earlier reproductive senescence [55▪]. During night shifts, those of morning chronotype had reduced peak, and less overall, melatonin production indicative of an attenuated nocturnal melatonin signal, than those of evening chronotype. Additionally, both morning chronotype and working rotating night schedules were positively associated with circulating estradiol, though not overnight melatonin, at the start of the day shift among Italian nurses [61]. Moreover, a recent Mendelian randomization study of chronotype and breast cancer risk provides compelling evidence for women with a morning preference, who – presumably – are more in line with a typical and most common 9–5 work day – exhibit lower risk of breast cancer than other chronotypes [102].

Alternatively, or in addition, younger women who work more demanding night shift schedules may experience more chronic fatigue and psychological stress, which has been linked with declining ovarian reserve [103,104]. The only other epidemiologic study to assess the impact of work-related exposures (beyond employment itself) on menopausal age supports job stress related to difficult schedules as a potential risk factor for early menopausal onset [105]. However, work schedules studied were not specific to night work.

CONCLUSION

Although night work is becoming an established risk factor for many adverse health outcomes, more research is needed to corroborate a causal link between these schedules and infertility or, more specifically, premature menopause. To date, there has only been one study investigating the effect of NSW on menopausal age [98▪▪]. Future work should focus on potential higher risk women, identified by factors such as chronotype, tobacco smoking and family history of earlier menopause or idiopathic premature ovarian failure, for which there soon may be informative genetic markers. Though, to date, there is insufficient evidence on which to base policy restricting night work for women, those already at elevated risk may best be served by selecting occupations without mandatory night work.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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