NIGHT WORK DURING PREGNANCY AND MATERNAL HEALTH

Paula Edeusa Cristina Hammer

PhD Thesis

This thesis has been submitted to the Graduate School of Health and Medical
Sciences, University of Copenhagen, December 2018

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Graduate School of Health and Medical Sciences,
University of Copenhagen

Department of Occupational and Environmental Medicine,
Bispebjerg and Frederiksberg University Hospital

2018

Author

Paula Edeusa Cristina Hammer, MD.

Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark

Academic advisors

Jens Peter Bonde, Professor, MD., DMSc.

Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark

Anne Helene Garde, Professor MSO, Cand. scient., Ph.D.

National Research Centre for the Working Environment, Copenhagen, Denmark

Ina Olmer Specht, MSc, Ph.D.

The Parker Institute, Bispebjerg and Frederiksberg University Hospital, Frederiksberg, Denmark

Sesilje Bondo Petersen, Ph.D.

Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark

Anja Bisgaard Pinborg, Professor, MD., DMSc.

Fertility Clinic, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Assessment Committee

Chairperson

Anne-Marie Nybo Andersen, Professor, MD.

Section of Social Medicine, Department of Public Health, The Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Assessor representing Danish research

Tine Brink Henriksen, Professor, Consultant, MD., Ph.D.

Department of Public Health and Department of Clinical Medicine, University of Aarhus, Aarhus, Denmark

Assessor from abroad representing international research

Mikko Härmä, Professor, MD., Ph.D.

Finnish Institute of Occupational Health, Finland

Preface and Acknowledgements

Night work during pregnancy…"*to work or not to work?*" When I set myself to investigate this question, I could not imagine how laborious, rewarding and joyful an experience this would be. Broadening my knowledge of the beautifully orchestrated and highly complex universe of circadian rhythm and pregnancy has humbled and amazed me. I feel therefore very honoured and privileged by the opportunity of having researched in this field within the last three years.

List of papers

Paper I (Published)

Night work and hypertensive disorders of pregnancy: a national register-based cohort study
Hammer P, Flachs E, Specht I, Pinborg A, Petersen S, Larsen A, Hougaard K, Hansen J, Hansen Å, Kolstad H, Garde A, Bonde JP.
Scand J Work Environ Health 2018;44(4):403-413. doi:10.5271/sjweh.3728

Paper II (in press, Journal of Occupational and Environmental Medicine)

Night work and sick leave during pregnancy: a national register-based within-worker cohort study
Hammer PEC, Garde AH, Begtrup LM, Flachs EM, Hansen J, Hansen ÅM, Hougaard KS, Kolstad HA, Larsen AD, Pinborg AB, Specht IO, Bonde JP.

Paper III (Submitted to the Scandinavian Journal of Work, Environment and Health)

Night work and severe postpartum depression: a national register-based cohort study
Hammer PEC, Hageman I, Garde AH, Begtrup LM, Flachs EM, Hansen J, Hansen ÅM, Hougaard KS, Kolstad HA, Larsen AD, Pinborg AB, Specht IO, Bonde JP.

Contents

Abbreviations

BMI = Body Mass Index

CI = Confidence Interval

CMD = Common Mental Disorders

DWHD = Danish Working Hour Database

HDP = Hypertensive Disorders of Pregnancy

ICD = International Classification of Diseases

OR = odds ratio

PPD = Postpartum Depression

RR = Relative Risk

SES = Socioeconomic Status

1. English summary

Around 10% and 14% of the female workers in Denmark and Europe, respectively, work at night, many of whom are at their childbearing age. Night work during pregnancy may induce sleep disorders along with hormonal changes resulting in several diseases both for the mother and the child. Therefore, the negative health effects of night work during pregnancy may have a major impact on public health and socioeconomic costs. The majority of previous studies in this field have used crude and self-reported information on working hours, and thus could not identify which aspects of night work are primarily related to negative health effects. The overall aim of the **PREGNIGHT** project was to use nationwide register-based information to: 1) investigate the impact of different dimensions of night work during pregnancy on the risk of hypertension and preeclampsia (HDP), sick leave, and severe postpartum depression (PPD); and 2) identify possible ways of organizing night work during pregnancy that might reduce its potential negative health effects. The dimensions of night work we investigated were: number and duration of night shifts, consecutive night shifts and short intervals between shifts.

The source population was identified from the Danish Working Hour Database, which contains nationwide payroll data from all public hospital employees in Denmark. We included all women who gave birth at least once in the period 2007-2015. The study cohort comprised approximately 20,000 women, where most were nurses (64%) or physicians (17%).

We found that more than 3 consecutive night shifts during the first 20 pregnancy weeks were associated with 41% increased risk of HDP (study I). If the pregnant woman was obese, all dimensions of night work increased the risk of HDP by 4-5-fold. In study II, we found that night shifts, especially those lasting more than 12 hours, and short shift intervals were associated with a 55% increased risk of sick leave during all pregnancy trimesters independent of personal factors (the participants were their own controls) when compared to day shifts. On the other hand, we found no increased risk of negative health effects among women who worked up to one night shift per week on average during pregnancy, as far as they did not have > 3 consecutive night shifts or were obese. If this result was to be false, the risks are expected to be rather small. In study III we did not find an overall increased risk of PPD in relation to night work. However, women who stopped working night shifts after the 1st trimester had an increased risk suggesting the presence of the healthy worker effect, where women somehow susceptible to PPD are selected out of night work earlier in pregnancy, while women with a relatively better health status continue working night shifts throughout pregnancy.

Our findings support the hypothesis that the health effects of night work are more related to the way night shifts are organized rather than the mere presence of night shifts.

If pregnant women work night shifts, adequate shift intervals along with reduction of their frequency and duration might reduce sick leave and HDP. Special attention must be paid to women who do not adapt to night work and those with other risk factors for pregnancy complications. All potentially modifiable risk factors for reproductive hazards must be taken into account by health care professionals who advise workers and employers on health risks of night work during pregnancy.

2. Danish summary

Det anslås, at 10% og 14% af kvinderne på arbejdsmarkedet i henholdsvis Denmark og Europa arbejder om natten, hvoraf mange er i deres fødedygtige alder. Natarbejde i løbet af graviditeten kan forårsage søvnforstyrrelser og hormonale ændringer medførende en række sygdomme både for moren og for barnet. Derfor kan de negative helbredseffekter af natarbejdet i løbet af graviditeten resultere i betydelige sundhedsrelaterede og socioøkonomiske omkostninger. De fleste tidligere studier på området har anvendt groft definerede og selvrapporterede oplysninger om natarbejde, og kunne dermed ikke identificere, hvilke specifikke aspekter ved natarbejdet der primært er associeret med negative helbredsudfald. Formålet med projekt **PREGNIGHT** var at anvende landsdækkende registerbaserede oplysninger om arbejdstider med henblik på: 1) at undersøge sammenhængen mellem forskellige aspekter ved natarbejde og risiko for forhøjet blodtryk og svangerskabsforgiftning, sygefravær og svær fødselsdepression; og 2) at identificere mulige måder at tilrettelægge natarbejde i løbet af graviditeten på, som kan mindske dets negative helbredseffekter. De forskellige aspekter af natarbejdet, som vi undersøgte, var: Antal og varighed af nattevagterne, antal nattevagter i træk og kort interval mellem vagterne.

Resultaterne er baseret på knap 20.000 kvinder identificeret fra den Danske Arbejdstids Database, fortrinsvist sygeplejersker (64%) og læger (17%), som fødte mindst én gang i perioden 2007-2015. Denne database indeholder detaljerede oplysninger om arbejdstid fra alle landets regionsansatte.

Vi fandt, at mere end 3 nattevagter i træk i løbet af de første 20 graviditetsuger øgede risikoen for hypertension og svangerskabsforgiftning med 41% (studie I). Hvis den gravide kvinde var svært overvægtig, var denne risiko 4-5 gange større ved alle aspekter af natarbejdet. I studie II fandt vi, at nattevagter, især vagter længere end 12 timer, samt kort vagtinterval øgede risikoen for sygefravær i det efterfølgende døgn med 55% i alle graviditets-trimestre sammenlignet med dagvagter. På den anden side fandt vi ikke nogen øget risiko for negative helbredsudfald blandt kvinder, som arbejdede op til én nattevagt om ugen i gennemsnit, såfremt de ikke havde mere end 3 nattevagter i træk eller var svært overvægtige. Hvis den risiko findes blandt disse kvinder, er den beskeden. I studie III fandt vi ikke overordnet øget risiko for svær fødselsdepression blandt natarbejderne. Derimod havde kvinder, som stoppede med at arbejde om natten efter 1. graviditets-trimester, en 2 gange øget risiko for fødselsdepression, hvilket indikerer en mulig *healthy worker*-effekt. Det betyder, at sårbare kvinder stoppede med at arbejde om natten tidligt i graviditeten, mens de relativt sundere kvinder fortsatte med natarbejde i løbet af graviditeten.

Vores resultater støtter hypotesen om, at de negative helbredseffekter af natarbejdet ikke blot handler om at have nattevagter eller ej, men er primært forbundet med måden hvorpå natarbejdet tilrettelægges.

Disse resultater giver anledning til overvejelser om, hvordan man skal rådgive arbejdspladser og gravide kvinder omkring tilrettelæggelse af natarbejde, hvor der er behov for fokus på både hyppighed og varighed af nattevagter i løbet af graviditeten.

3. Introduction

" Sleep oh blessed sleep
the place where I can dream
of all that I do need
my energy to keep

Sleep oh blessed sleep
lull me with your content
keep med ever safe
my soul's sanity to keep

Sleep oh blessed sleep,
let me emerge at morn
with clearer thought and mind
with no more need to weep."

by Susan Alldred-Lugton

Health effects of sleep surpass the ability to "restore the body's energy and clear the mind". Adequate rest and sleep synchronized with the day/night cycle determined by sunlight contributes to the optimal function of all organs and systems and is tightly coordinated by several complex processes acting already during the intrauterine life. Disturbances of this synchronization result inevitably in physiological changes that might lead to disease. Night work is one of many factors that can induce such changes. The focus of the ***PREGNIGHT*** project, which is the base for this thesis, is the impact of night work during pregnancy on maternal health.

Pregnant workers, employers, health care professionals and police makers in public health should find this thesis particularly relevant for at least three reasons:

1. Many occupations with night work, such as hospital employees and cabin crew, have a high proportion of female workers in their reproductive age from all socioeconomic levels. According to the 6th European Working Conditions Survey published by the European Foundation for the Improvement of Living and Working Conditions in 2016, 14% of the female workers reported working at night (≥ 2 hours of work between 22:00 and 05:00) at least once a month (1).

2. If maternal health is negatively affected by night work during pregnancy, this would affect not only the mother and her child in the perinatal period, but also the whole family in a long-term period, having therefore potential consequences for public health in general.

3. Negatively affected maternal health can also have considerable socioeconomic implications for the large proportion of economically active population represented by women in reproductive age, such as difficulties returning to work or keeping attachment to the labor market.

4. Background

Circadian rhythm

Circadian (from Latin *circa* = around, *dies* = day) rhythm refers to the fluctuations of human physiological processes of approximately 24 hours. It is controlled by the suprachiasmatic nucleus of the hypothalamus in the brain, also called the biological master or central clock, through both the autonomic nerve system and hormones (2, 3). Several hormones including melatonin, insulin, cortisol, cholesterol, growth factors, gonadotropins and sex hormones participate in circadian regulation but the complexity of their endocrine actions is not fully understood (4). Light reaching the retina is the primary environmental cue for the circadian rhythm. However, peripheral tissues present their own peripheral clocks controlled by clock genes independent of light (3, 4) – see figure 1. Thus, circadian regulation depends on several complex and highly coordinated processes that mutually influence each other (5). For instance, food intake, exercise, body temperature and sleep can also regulate circadian fluctuations of peripheral clocks.
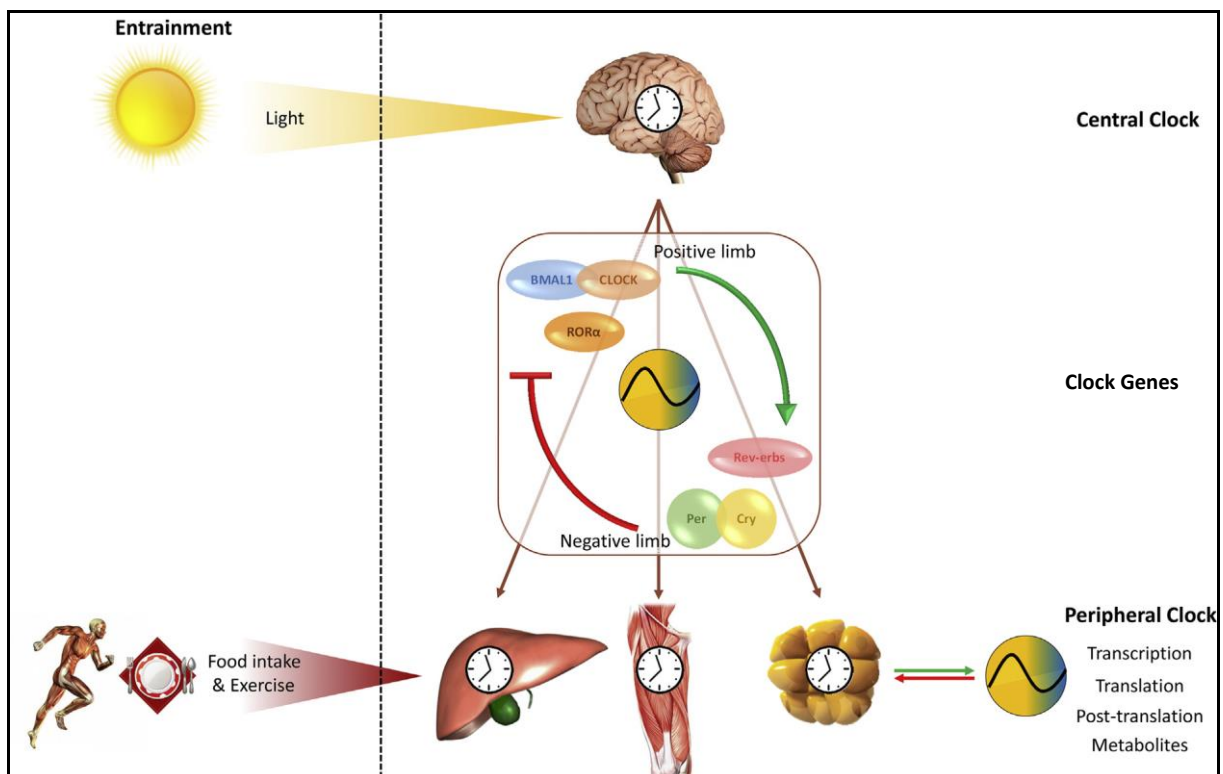
Figure 1 – The circadian clock organization in humans. Clock genes expressed in all tissues control positive and negative transcription factors with feedback loops. The central clock adjusts the clock pace to the day/night cycle. It synchronizes rhythms generated by peripheral clocks creating an internal alignment. In addition, the peripheral clocks are responsive to nutrients and exercise. Modified from Mayeuf-Louchart A, Zecchin M, Staels B and Duez H. Circadian control of metabolism and pathological consequences of clock perturbations. Biochimie (2017) (3).

Circadian regulation of reproduction

Circadian regulation occurs in all processes of human reproduction. In women it coordinates the release of gonadotropins in the brain, the production of sex hormones by the ovaries, the ovulation, the development of pregnancy, and the complex interaction of the maternal and fetal biological rhythms – see figure 2 (6-9).

Gonadotropins   **Sex hormones**   **Fertilization**   **Human chorionic gonadotropin Progesterone Oxytocin**

CIRCADIAN REGULATION OF REPRODUCTION
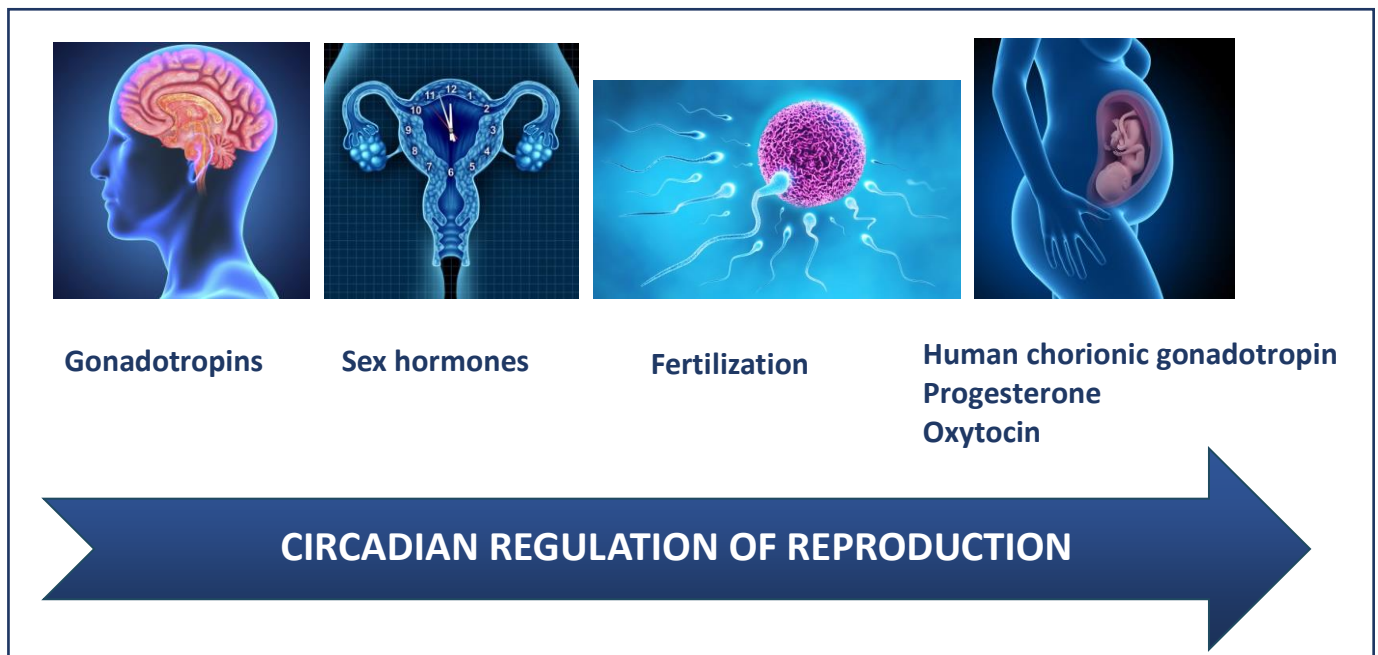
Figure 2 – Circadian regulation occurs in all processes of human reproduction, before, during and after conception. Royalty-free images from www.dreamstime.com

Melatonin, a neuroendocrine hormone, is recognized as crucial for the circadian regulation of all biological systems (10), including human reproduction (9, 11-13). It is secreted primarily by the pineal gland during the night, but an increasing number of studies within the last 10 years have shown that it is also produced in peripheral tissues such as ovaries and placenta (14-18). This is in accordance with findings of melatonin levels increasing progressively throughout pregnancy with peak levels during the 3rd pregnancy trimester – see figure 3 (19-22). It is still unknown whether melatonin produced at peripheral tissues contributes to the elevated systemic levels observed in pregnancy, but this seems to be the case at least for placental melatonin (15).
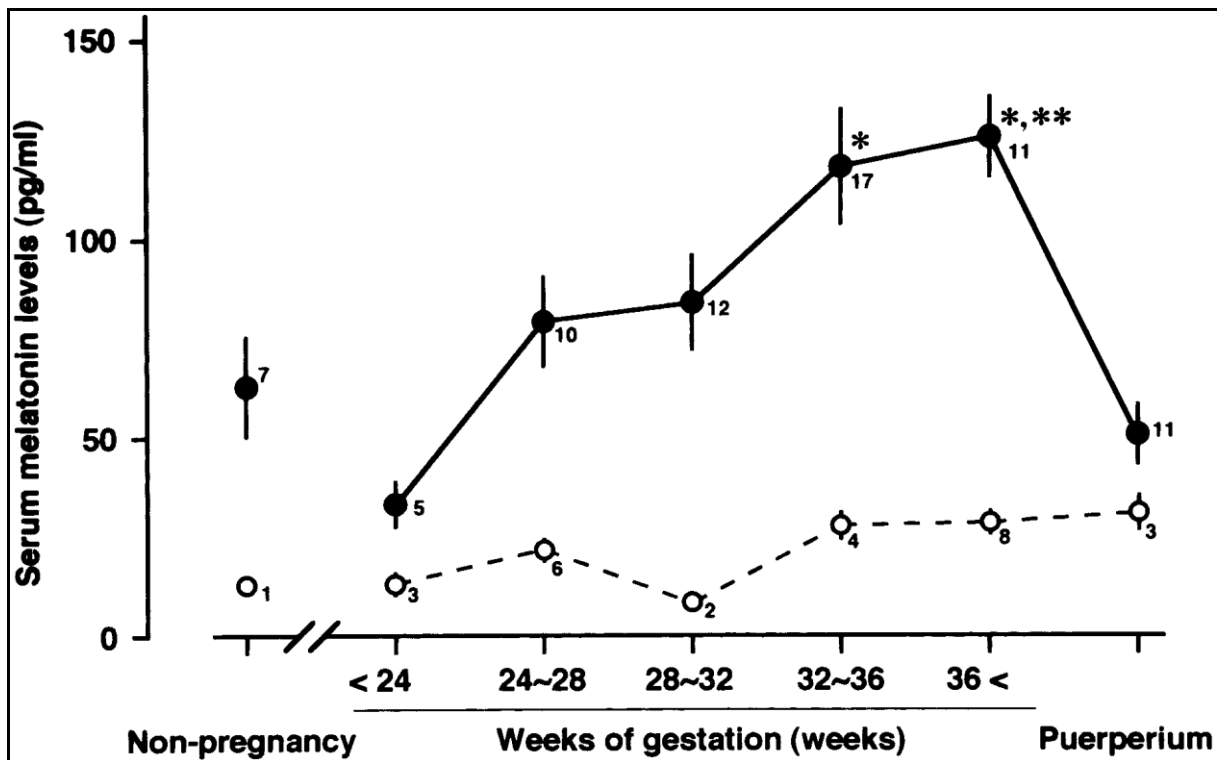
Figure 3 – Levels of maternal serum melatonin during the night (solid line) and day (dotted line) in singleton pregnancies. Values are means ± standard error of the mean for the number of patients indicated beside each point. * refers to p < 0.01 compared to non-pregnancy values and ** refers to p < 0.05 compared to 24-28-week values.
From Nakamura et al. Changes of serum melatonin level and its relationship to feto-placental unit during pregnancy. Journal of Pineal Research (2001) (21).

Melatonin acts as an autocrine and paracrine hormone, through membrane and nuclear receptors, and directly as a free radical scavenger (23, 24). For instance, melatonin seems to act in the ovary preventing oxidative stress during oocyte maturation, ovulation and embryo development (14, 17, 25, 26). This knowledge has been supported by studies showing improvement of fertilization and pregnancy rates in medically assisted reproduction (27, 28). Melatonin's potent antioxidant actions has been extensively studied in relation to several disorders also among men and non-pregnant women (29).

Melatonin's role in the placenta has been gradually unraveled since the discovery of enzymes responsible for production of melatonin along with membrane and nuclear receptors of melatonin in several human placental cell lines (18, 30). Melatonin is believed to assist the turnover of the villous trophoblast, i.e. the barrier between the mother and the fetus, which is crucial for the maintenance of a normal pregnancy (16, 31, 32). This turnover happens continuously throughout pregnancy and is dependent on tightly coordinated pro- and anti-apoptotic cellular processes (33). Interestingly, melatonin has found to inhibit

apoptosis in normal cells and induce apoptosis in cancer cells (15, 34, 35). This dual apoptotic function of melatonin has been explored in cancer research (23, 36).

The current evidence suggests that melatonin may also play an important role in induction of parturition, the process of labor and delivery of a childbirth (15), possibly through immunological processes (37). This is in line with findings of melatonin receptors in uterine muscle cells (38), where the melatonin levels peaking at the end of pregnancy (21), and the onset of human labor more frequently occurring during the night or early morning (39). There is indeed evidence suggesting that melatonin exerts synergy with oxytocin in promoting strong and coordinated uterine contractions (15, 39).

Overall, the current evidence suggests that melatonin during pregnancy exerts antioxidant, anti-inflammatory, and immunomodulatory actions contributing to placental physiology, parturition, and regulation of the fetal circadian rhythm (37, 40-44). Melatonin may also play a role in developmental programming of diseases (45). It is not surprising that melatonin has been considered the "Higgs boson of human reproduction unlocking the mysteries of fertility" (46). However, it is important to keep in mind that circadian regulation of reproduction involves much more than the melatonin's actions, for instance the regulation of clock genes in relation to fertility, placental function and parturition (7, 8, 47, 48). On the other hand, considering the extent of melatonin's involvement in physiological processes and the feasibility of measuring melatonin levels compared to assessing clock genes activity makes melatonin a useful tool to widen our knowledge of the circadian regulation.

Night work as a reproductive hazard

Considering the crucial role of circadian regulation in human reproduction we asked ourselves how circadian disruption affects reproductive health. As previously mentioned, circadian regulation depends on the coordination between biological timing (processes regulated by the central master clock and peripheral tissue clocks) and behaviors (such as sleep, food intake and exercise) (2-4). Circadian disruption can therefore be defined as desynchronization between biological timing and behaviors, which influence each other mutually.

The way night work is believed to induce circadian disruption is through disturbance both of signaling from the master clock (light exposure during the night) and of behavior (wakefulness, physical activity, and food intake during the night) (49, 50). For example, a recently published study among 341 Danish workers, where the majority were hospital employees, revealed that night workers had 16% lower salivary melatonin levels compared with day workers on work days, while no differences were observed in days off (51). It is not surprising that exposure to light at night has been called an environmental endocrine disruptor (52). Accordingly, night work has been associated with sleep disorders – commonly called shift work sleep disorder – as well as metabolic, immunological, cardiovascular and

neuroendocrine disturbances (50, 53, 54). For example, a Nationwide 3-year follow-up study of nursing students concluding their education in Sweden showed consistent and progressive decline of sleep quality after entering working life due to the combination of night work and psychosocial stressors (55).

Several studies have shown the role of night work as a potential reproductive hazard in relation to menstrual cycle disturbances, time-to-pregnancy, miscarriage, low-birth weight, and preterm birth (56-60). Night work during pregnancy might potentially be even more harmful as pregnancy itself imposes physiologically altered sleep and fatigue along with complex hormonal and immunological changes (61-64).

In contrast to the majority of earlier studies which investigated fetal outcomes, like birth weight and preterm birth, in relation to night work during pregnancy (44, 56, 57, 59, 60) the focus of this thesis is the mother's health.

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP), which includes gestational hypertension, preeclampsia and eclampsia, are among the leading causes of perinatal mortality both of the mother and the child in developing countries affecting around 8% of pregnancies worldwide (65-67). Even though the pathophysiology of HDP is not completely understood, it is known to involve complex interactions between maternal, fetal and placental factors (68-71). Identifying potentially modifiable risk factors, such as night work, is of crucial importance.

Blood pressure is influenced by circadian regulation with the lowest levels during night time (72, 73). This is for instance why the time of day for taking an anti-hypertensive medication is important to achieve adequate control of blood pressure. Both disturbances of melatonin levels and sleep disorders were found to alter blood pressure patterns in pregnancy (74, 75). Interestingly, not only melatonin levels, but also melatonin-synthesizing enzymes and melatonin receptors were found to be decreased in the placenta of women with preeclampsia (15, 21, 76). It is therefore possible that placental melatonin might be involved in the pathogenesis of preeclampsia. This hypothesis is further supported by the central role of oxidative stress in preeclampsia in contrast with melatonin's role as a potent antioxidant (32, 77, 78). For this reason, several studies have investigated the use of melatonin to treat preeclampsia (79, 80). Further, there is some evidence of disturbances of maternal melatonin levels contributing to programmed hypertension of the offspring in the adult life through epigenetic regulation (81).

Besides hormonal changes, night work can be associated with HDP also through behavioral factors such as disturbed sleep, smoking habits and diet, which are known risk factors for cardiovascular diseases (82-88).

Prior studies of the association between shift work and HDP have found conflicting results.

Within a Finnish case-control study of congenital malformations, a nested-cohort study in the matched control group (N=368) investigated the association between shift work (defined as two- or three-shift schedules or other unspecified types of shift work) during pregnancy and pregnancy-induced hypertension. Analysis adjusted for age, parity, outcome of previous pregnancies, alcohol intake, and smoking revealed a non-statistically significant 20% increased risk of pregnancy-induced hypertension (relative risk [RR] 1.2, 95% confidence interval [CI] 0.7-2.0) among women participating in shift work compared to day work (89). A cross-sectional survey of 3,321 Norwegian women who gave birth within a 6-week period found a two-fold increased risk of preeclampsia (odds ratio [OR] 2.0, 95% CI 1.1-3.6) among those who reported having shift work (yes/no; not further specified) (90). The analysis was adjusted for age, parity, body mass index (BMI), education, and smoking. However, a case-control study among a random sample of 4,582 women from Quebec showed no association between night work (≥ 1 hour of night work per week) and the risk of preeclampsia or gestational hypertension OR 1.0, 95% CI 0.5-2.0 (adjusted for age, parity, history of abortion, level of education, BMI, smoking and leisure-time physical activity) (91). Likewise, another cross-sectional study of 24,200 women in Taiwan found no association between rotating shifts (other than fixed evening or day and evening shifts) and the risk of gestational hypertension and preeclampsia after adjusting for age, ethnicity, education, marital status, parity, BMI, previous abortion, smoking and alcohol drinking (OR 0.78, 95% CI 0.44-1.41). Finally, in a birth cohort study (N=4,465) of physically demanding work and occupational exposure to chemicals, working night shifts 'occasionally, often or very often' appeared almost protective of pregnancy induced hypertension (OR 0.59, 95% CI 0.25-1.42) or preeclampsia (OR 0.86, 95% CI 0.26-2.80) although this was not statistically significant (92). These analyses were adjusted for age, pre-pregnancy BMI, education, ethnicity and parity. A possible explanation for such findings was the low prevalence of HDP in their study (139 cases), combined with the low prevalence of the various occupational risk factors they investigated.

All these studies share the main limitation of using a crude and self-reported assessment of working hours. In some studies, it was not even possible to determine whether their definition of shift work included night shifts (89, 90). Further, with exception of one study (92), the information was collected retrospectively. As a result, these studies were not able to analyze different dimensions of night work or pregnancy period-specific effects. This is relevant for at least three reasons. First, night work early in pregnancy is of crucial interest, as HDP is related to disturbances of placental development (68). Second, different working time schedules have shown to have different effect on health and work-life balance (93). Third, the validity of self-reported exposure to shift work varies across different schedules (94).

In study I we addressed these shortcomings by investigating the association of HDP with different dimensions of night work during the first 20 pregnancy weeks, i.e. in the time window prior to the clinical diagnose of HDP.

Sick leave during pregnancy

Besides the aforementioned physiological changes, night work might affect health negatively through fatigue due to disturbed sleep (including sleep length and quality) and/or combination of night work with physically or psychosocially demanding work (53, 95-97). Furthermore, even when a night worker does not experience sleep disturbances, other factors such as work-life conflicts affecting family life and social relationships can result in lack of recovery and hereby fatigue (98, 99). Accordingly, shift work has been identified as an independent risk factor for sick leave (100) and fatigue seems to play an important role in this association. For instance, in a 2-year prospective cohort study of truck drivers (N=526), those who reported high baseline need for recovery after work presented increased risk of sick leave (OR 2.19, 95% CI 1.13-4.24 adjusted) (101); and a study of a representative national sample of shift worker in Sweden (N=2,031) found that night work was associated with fatigue (OR 1.75, 95% CI 1.35-2.27) and disturbed sleep (OR 2.75, 95% CI 2.13-3.57) (93).

These negative effects of night work are especially relevant for pregnant workers as many of them suffer from fatigue and disturbed sleep due to physiological changes such as heartburn, nocturnal urination, musculoskeletal discomfort and shortness of breath (61-64). As a result, fatigue is a common cause of sick leave among pregnant women (102, 103). In this sense, sick leave can be seen as a mean of achieving recovery, especially if the woman is entitled to paid sick leave (104). High rates of sick leave among European pregnant workers have indeed been shown (104-106). For instance, a recent studies showed prevalence of sick leave of 56%, 62% and 71% of employed pregnant women in Denmark, Norway and Poland, respectively (104, 105). In around 10% of the cases work-related factors were reported as the primary reason for sick leave (104, 105).

In prior studies, associations have been found between night work during pregnancy and increased risk of sick leave. In a cross-sectional study of 773 Danish hospital employees, night or shift work (yes/no) was associated with increased risk of sick leave corresponding to 10% of the schedule working time (OR 1.4, 95% CI 1.0-1.9 adjusted for age, occupation, full- or part-time job and previous sick leave) (107). This result is supported by another Danish cohort study (N=51,874) where women with shift work including night shifts were at increased risk of sick leave of > 15 days (hazard ratio 1.61, 95% CI 1.42-1.83) (108). Furthermore, they found a positive trend showing increased risk with increasing number of monthly night shifts among women with > 8 night shifts per pregnancy month (HR 1.89, 95% CI 1.67-2.15). A cross-sectional study of 1,495 French women who returned to work after maternity leave revealed that having worked at least one night shift during pregnancy was associated with sick leave of any duration (109). As night work was investigated combined with other occupational exposures (ergonomic, chemical, biological and radiation) there were no estimates for the effect of night work independently. A survey of 508 women receiving antenatal care at a Danish hospital showed that women who worked evening and/or night shifts (yes/no) during pregnancy reported sick leave of > 20 days more

frequently (P=0.04), however, shift work was not a predictor of sick leave (OR 1.3, 95% CI 0.8-2.2 adjusted for age, parity, BMI, education, conception, low back pain, disorders, exercise, work conditions and work hours) (105). The non-statistically significant result might be a consequence of low power, as the study population was relatively small.

Definitions of short- and long-term sick leave are contextual and vary widely. They can for example refer to total days of sick leave within a specified period or to the duration (number of consecutive days) of the single sick leave periods. It is possible that short- and long-term sick leave during pregnancy in relation to night work involve different factors. For example, long-term sick leave might be primarily associated with pregnancy complications while fatigue and lack of recovery might play a more important role in short-term sick leave. On the other hand, it is plausible that chronic fatigue might as well increase the risk of long-term sick leave. This waits however to be proven.

A systematic review on the association of shift work with sick leave from 2012 pointed out that this association is schedule specific (100). This is not surprising, as evening and night shifts for instance affect sleep and work-life balance differently. Some studies have indeed shown different effects on sleep and fatigue of different types of shifts (93, 110-112). Therefore, it is important to obtain precise and detailed information on work schedules to appropriately evaluate their health effects. This was not the case for any of the previous studies of sick leave during pregnancy in relation to night work, as they all used self-reported information on working hours.

Studies of sick leave comparing different individuals are influenced by several personal factors that cannot be fully accounted for in statistical analyses, which may bias the quantification of the effects of night work on sick leave. Furthermore, most of those studies analyzed workers with sick leave composed by several periods of short duration along with workers with sick leave composed by one or few periods of long duration. As a result, they were not able to evaluate the effect of night work on sick leave for those who continued to work throughout pregnancy. This is relevant for identification of potential interventions to reduce sick leave among these women. In study II, we attempted to overcome these limitations by using the workers as their own controls and stratifying the analyses per pregnancy trimester.

Postpartum depression

Postpartum depression (PPD) is defined as the occurrence of major depressive symptoms up to 12 months postpartum (113). Its prevalence is estimated to 10-15%, but higher rates have been reported across countries (114) making PPD to be considered a global public health problem (115). The potential severe consequences of PPD include suicide and infanticide (116).

The pathophysiology of PPD is not completely understood, but it involves complex interactions between biological, genetic and psychosocial factors (117). Established strong risk factors are prior own or family history of depression, but adverse life events, lack of social support and low socioeconomic status (SES) play also an important role (118-121).

Night work might be a risk factor for PPD through neuroendocrine dysfunction and sleep disorders. For instance, the precursor of melatonin – the neurotransmitter serotonin – is known to be deficient in depression and melatonin is involved in the epigenetic regulation of serotonin metabolism (122). Accordingly, lower melatonin levels were observed among depressed pregnant women (123). Further, melatonin is a potent anti-inflammatory and inflammation seems to be associated with perinatal depression (124). Sleep disturbance both during pregnancy and in the postpartum period is closely associated with PPD (125). However, to what extent sleep disorders are predictors or mediators of the development of PPD is not completely understood.

A recent meta-analysis of five longitudinal studies with follow-up ≥ 2 years found a RR of depression 1.42 (95% CI 0.92-2.19) among male and female night workers (126). Another systematic review of eight cross-sectional and three longitudinal studies found a RR of 1.43 (95% CI 1.24-1.64) across sex, night work duration, type of occupation, continent and type of publication (127). To our knowledge no studies have addressed PPD, but cases of PPD might be included in the study populations, especially when depression is self-reported, as PPD can occur until one year postpartum.

Overall, previous studies of depression in relation to night work are challenged by cross-sectional design, crude exposure assessment, and self-reported outcome. As a contrast, instead of self-reported depressive symptoms, we investigated the risk of severe PPD in study III, which is PPD medically diagnosed at a hospital. In addition, most of these studies did not account for the possibility of the healthy worker survivor effect, i.e. the selection of individuals with poorer health status out of night work (128, 129). Both in study I and III we explored the possibility of healthy worker survivor effect by changes of work schedules during pregnancy.

5. Aim of this thesis

The overall aim of the ***PREGNIGHT*** project was to investigate the effect of different dimensions of night work during pregnancy on maternal health, and furthermore to identify possible ways of organizing night work during pregnancy that might reduce its potential negative health effects, using nationwide register-based information in a prospective design.

The specific objectives were to investigate:

    I.   The risk of hypertensive disorders of pregnancy in relation to number and duration of night shifts, consecutive night shifts and quick returns during the first 20 pregnancy weeks both in comparisons with day workers and within-night workers;

    II.   The risk of sick leave starting within 24-hours after night shifts of different duration compared with day shifts using the workers as their own controls; and

    III.   The risk of severe postpartum depression in relation to number and duration of night shifts, consecutive night shifts and quick returns during the first 32 pregnancy weeks both in comparisons with day workers and within-night workers.

6. Methods

6.1 Design

We conducted a nationwide prospective cohort based on four Danish national registers:

1) **The Danish Working Hour Database (DWHD) (130)**, a national payroll database covering more than 250,000 employees in the Danish administrative regions including all hospital employees, provided the source population. The DWHD provides information on date and time of start and end of shifts and all types of paid and unpaid leave, job title and place of employment form January 2007 to December 2015. As the DWHD makes the base to salary payment, the validity of the timing of working hours is considered high. However, duration of shifts and weekly working hours may be underestimated for occupations with common occurrence of unpaid extra working hours, such as physicians (130).

2) **The Danish Medical Birth Register (131)**, which contains information on all births in Denmark since 1973, provided demographic characteristics and pregnancy information, such as the mother's BMI, age and smoking habits, and the child's date of birth and gestational length. Validity of such information is considered very high,

as this register covers all hospital and home births in Denmark and some of these variables are drawn directly from the Civil Registration System (131).

3) **The Danish National Patient Register (132)**, which contains data on hospital admissions since 1977 and on outpatient since 1994, provided information on the outcome and other relevant diseases for study I on HDP. This register has been found to have high data quality, i.e. high levels of validity and completeness, for severe diagnoses in general (131, 132). However, validation studies of discharge diagnoses for HDP have shown high specificity, but low sensitivity due to misclassification (133).

4) **The Danish Psychiatric Central Research Register (134)**, which contains data on psychiatric inpatient treatment since 1969 and on outpatient treatment since 1995, provided information on the outcome and other relevant diseases for study III on PPD. This register has also shown high validity of data for severe diagnoses, such as severe PPD. Nevertheless, is important to notice that most cases of mild to moderated mental disorders are diagnosed and treated by general practitioners or private psychiatry specialists, and thus not registered in the Danish Psychiatric Central Register (134).

We performed data linkage on individual level through the civil registration number given to all residents in Denmark since 1968. All data was anonymized by Statistics Denmark, which also provided the digital platform to all data handling and analyses, ensuring data safety according to the Danish Data Protection Legislation.

6.2 Ethical approval

The study was approved by The Danish Data Protection Agency (journal no. BFH-2015-079, I-Suite no. 04228) and The Danish Administrative Regions.

6.3 Source Population

The source population were women from the DWHD who gave birth at least once between 2007 and 2013 for the studies of HDP and sick leave (N= 42,485), and between 2007 and 2015 for the study on PPD (N=43,833 women contributing with 70,306 births). The following numbers refer to the latter study. We excluded women ≤ 18 and ≥ 50 years (N=16 pregnancies); multiple pregnancies (N=3243); and pregnancies conceived in 2006 (N=6383), because they lacked payroll data, and thereby exposure data, from conception to January 2007.

6.4 Study Cohort

Study I

For identification of the cohort for the study of HDP we further excluded pregnancies from women without registration in the DWHD of any night or day shift during the first 20 pregnancy weeks (N=26,481). This was the exposure time because gestational hypertension is by definition diagnosed after 20 pregnancy weeks (68). To avoid clustering effects each woman contributed with only their first pregnancy occurring during the study period (N=5902 pregnancies excluded), leaving 18,724 women with singleton pregnancies eligible for analysis.

Study II

For identification of the cohort for the study of sick leave we further excluded pregnancies whose employment in one the administrative regions of Denmark, i.e. registration in the DWHD, started after conception or ended before 32 pregnancy weeks (N=16,570) to ensure that payroll data was available throughout pregnancy. We applied the cut-off of 32 pregnancy weeks because most of the workers in the study cohort were entitled to pregnancy leave eight weeks prior to their due date (135-137). As we conducted fixed effects analysis, which requires change in both the exposure and the outcome for each participant (138), the study population comprised women with both ≥ 1 day shift, ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks (N=23,024 excluded). Finally, each woman contributed with only their first pregnancy occurring during the study period (N=1714 pregnancies excluded), leaving 9799 women with singleton pregnancies eligible for analysis.

Study III

For identification of the cohort for the study of PPD we further excluded pregnancies resulting in still births (N=254); and pregnancies without at least one day or night shift during the first 32 pregnancy weeks (N=4954). To ensure that payroll data was available throughout pregnancy, we excluded pregnancies with registration in the DWHD starting after conception or ending before 32 pregnancy weeks (N=25 330). Finally, we excluded pregnancies with other work schedules than fixed day shifts or at least one night shift during the first 32 pregnancy weeks (N=5117), for example fixed evening shifts, leaving 19,382 women with 25,009 singleton pregnancies eligible for analysis.

6.5 Demographic information

- ➤ Age in categories of < 30, 30-35 or > 35 years. The cut-off of > 35 years for the oldest category was based on prior studies showing higher risk of pregnancy complications among this age group (139).
- ➤ BMI in categories of < 24.9, 25.0-29.9 or ≥ 30 kg/m^2 corresponded to the classification proposed by The World Health Organization (140).
- ➤ Parity in categories of 1, 2 or ≥ 3.
- ➤ Smoking in categories of nonsmoker, former smoker or smoker.

The variables mentioned above derived from The Danish Medical Birth Registry, and corresponded to what was registered by the midwife or family doctor at the first antenatal visit.

- ➤ The classification of SES (high, medium, low) derived from Statistics Denmark and was based on the two Danish versions of the International Standard Classification of Occupations from 2007-2009 and 2010-2015 (ISCO-88 and ISCO-08), respectively (141, 142).

6.6 Exposure assessment

Exposure time

The exposure time for the respective pregnancy started at conception date, which was calculated subtracting gestational length in days from the child's birth date. To allow assessment of pregnancy period-specific exposure number and duration of shifts and days of sick leave were distributed per pregnancy week – see figure 4.

Number and duration of shifts and sick leave distributed per pregnancy week

Conception

Birth
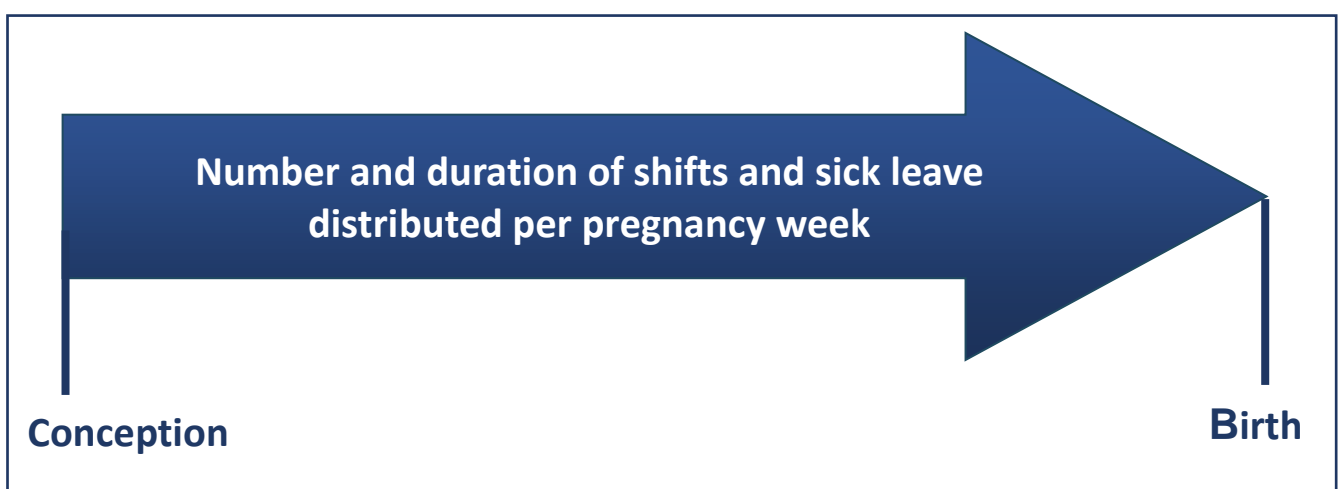
Figure 4 - Assessment of pregnancy period-specific working time exposure in the *PREGNIGHT* studies.

Definition of night work and night shifts

Night work in this thesis refers to shift work including night shifts.
Shifts, including on-call shifts, lasting ≥ 3 hours were defined as day (start time after 06:00 and end time before 21:00) or night shifts (any start and end time including any duration of working hours between 23:00 and 06:00) following the definition of prior studies using the DWHD (143).
The different dimensions of night work were expressed by number and duration of night shifts, consecutive night shifts and quick returns as defined below.

Number of night shifts: The cumulated number of night shifts was 1-19 or ≥ 20 night shifts (roughly corresponding to ≥ 1 night shift per week on average during the first 20 pregnancy weeks) on study I; and 1-8 or ≥ 9 (roughly corresponding to > 1 night shift per month on average during the first 32 pregnancy weeks) on study III. The reason for the lower cut-off in study III was the low number of cases of PPD across exposure categories.

Duration of night shifts: The duration of night shifts was defined as ≤ 8 hours, > 8-12 hours or > 12 hours (long night shifts).

Consecutive night shifts: Categories of consecutive night shifts were either only single night shifts, at least one spell of 2-3 consecutive night shifts and no spells of > 3 consecutive night shifts, or at least one spell of > 3 consecutive night shifts during the respective exposure time.

Quick returns: We defined quick returns as intervals of < 11 hours between any type of shifts or of < 28 hours after a night. The cumulated number of quick returns was categorized as 0 (night work without quick return), 1-4 or ≥ 5 quick returns (roughly corresponding to ≥ 1 quick return per month on average during the first 20 pregnancy weeks); and 1-8 or ≥ 9 quick returns (roughly corresponding to ≥ 1 quick return per month on average during the first 32 pregnancy weeks).

The choice of these dimensions and the respective cut-offs was based on a pioneer study using payroll data of nurses and physicians in Finland (144). This study proposed algorithms for register-based epidemiological studies using the following working time patterns, which were characterized as potentially related to negative health effects: 1) length of the working hours; 2) time of the day; 3) shift intensity; and 4) social aspects of the working hours. The latter was the only dimension that we did not investigated in our studies. These social aspects were related to the proportion of weekend work, days off and wished shifts, and to the variability of shift starting and ending times.
The cut-off of < 11 hours for quick returns followed the definition proposed by the European Union's Working Time Directive (145).

6.7 Outcome assessment

Hypertensive disorders of pregnancy: for study I the outcomes was retrieved from the Danish National Patient Register and was defined by the following International Classification of Diseases, 10th revision (146) (ICD-10) codes: I10-15 (hypertension), O12,13,16 (gestational hypertension) or O14,15 (pre-eclampsia and eclampsia).

Sick leave: for study II the outcomes was a registration of sick leave in the DWHD lasting ≥ 3 hours. Registrations of sick leave with consecutive dates were collapsed with the date of the first and last registration defining the duration of the sick leave period. We defined registrations in the DWHD of 'exacerbated pregnancy symptoms' or 'pregnancy complications' as pregnancy leave. These registrations were used for descriptive purposes to assess the total absence during pregnancy and in sensitivity analysis as they reflected pregnancy leave mostly due to medical complications and not ordinary sick leave. Administrative procedures for registration of pregnancy leave differ from registrations of sick leave in our cohort, and they vary across the five administrative Regions of Denmark. Registrations of pregnancy leave were therefore not appropriate to investigate the risk of calling in sick within 24 hours after a shift.

Severe postpartum depression: for study III the outcome was retrieved from the Danish National Patient Register and the Danish Psychiatric Central Research Register and was defined as ICD-8 codes 296.0 (involutional melancholia) and 300.4 (depressive neurosis) or ICD-10 codes F32 (depressive episode) and F33 (recurrent depressive disorder) registered as the primary diagnose at somatic or psychiatric hospital departments either as in- or outpatient treatment.

The dates of registration of the respective diagnose were classified as prior to pregnancy (from 1969 to the day before conception date), during pregnancy (from conception to birth date) or postpartum (within one year after the date of birth) in relation to each pregnancy.

6.8 Statistical Analysis

Study I

Statistical model. Logistic regression of the relative risk of HDP by different dimensions of night work during the first 20 pregnancy weeks. Results were presented for crude and adjusted analysis (adjusted for age, BMI, parity, smoking, SES and sick leave three months prior to pregnancy; and further adjustment for number of night shifts in the analysis of consecutive night shifts, quick returns and duration of night shifts). Sick leave three months prior to pregnancy (0, < 10 or ≥ 10 days) was the sum of all days registered as sick leave lasting ≥ 3 hours within three months prior to conception date. Missing values of sick leave three months prior to pregnancy (8%) corresponded to women whose employment covered

by the DWHD started < 3 months prior to conception date. Because of too few cases across exposure categories, it was not possible to adjust the analyses for cases of prior hypertension (N=44), prior HDP (N=287), prior diabetes (N=17) or current gestational diabetes (N=202).

Reference group. In all analyses we made comparisons both of night work (≥ 1 night shift) versus day work (fixed day shifts) and, within night work, of the lowest versus the highest categories of exposure during the first 20 pregnancy weeks.

Interaction analyses. We investigated whether the association between night work and HPD was modified by age, BMI and SES.

Sensitivity analyses. We performed sensitivity analyses restricted to nulliparous women (N=9,660); with pre-eclampsia as the outcome; and restricted to the 1st trimester (12 weeks) as the exposure time (N=18,158).

Study II

Statistical model. We compared the risk of sick leave of any duration starting within 24 hours after night shifts of different length versus day shifts during the first 32 pregnancy weeks using the participants as their own controls. We performed fixed effects logistic regression to account for repeated measures within workers. This statistical method requires that each participant has change in both the exposure and the outcome, as it in praxis, answers the question: "Does a change in the exposure cause a change in the outcome?" (138). This statistical method was not appropriate to investigate consecutive night shifts and quick returns.

Interaction analyses. We considered age, BMI and occupation as potential effect modifiers. The reason for the latter is that different occupations have different organization of working hours and work content, i.e. different tasks and workload. As nurses and physicians represented most of the cohort, we limited stratified analyses to these occupations.

Sensitivity analyses. We performed sensitivity analyses restricted to nulliparous women (N=5,095) and using both sick leave and pregnancy leave as the outcome.

Study III

Statistical model. Logistic regression of the relative risk of PPD by different dimensions of night work during the first 32 pregnancy weeks. We applied generalized estimating equations to account for repeated pregnancies within participants. Results were presented for crude and adjusted analysis (adjusted for age, BMI, parity, SES, sick leave three months

prior to pregnancy and prior diagnosed severe depression). Prior diagnosed severe depression (yes/no) derived from the Danish National Patient Registry and the Danish Psychiatric Central Research Registry.

Reference group. In all analyses we made comparisons both of night work (≥ 1 night shift) versus day work (fixed day shifts) and, within night work, of the lowest versus the highest categories of exposure during the first 32 pregnancy weeks.

Sensitivity analyses. We performed sensitivity analyses restricted to nulliparous women (N=9,332); restricted to pregnancies without prior diagnosed severe depression (N=24,582); restricted to nurses (N=11,298), who represented most of the cohort; and within-night work analysis with restriction to night work during the 1st or 1st and 2nd trimester compared to night work throughout pregnancy. The reason for the latter was to evaluate the potential presence of healthy worker survivor effect in the main analysis. In another words, the possibility of women somehow susceptible to PPD stop working night shifts during pregnancy and, therefore, not contributing to the group of workers with the highest cumulated exposure to night work.

See table 1 for an overview of the study designs in the three studies of the ***PREGNIGHT*** project. In all studies the results were presented as OR with 95% CI. For interaction analyses we used a likelihood ratio test comparing models with and without a multiplicative interaction term (the product of the combined effect). We used two-tailed tests with a significance level of 0.05. All analyses were done with the SAS 9.4 software (SAS Institute, Cary, North Carolina, United States) through the Statistics Denmark's digital platform.

Table 1 – Overview of the study designs in the three studies of the *PREGNIGHT* project.

Study	Cohort	Exposure	Covariates	Outcome	Statistical Analysis
I – Night work and hypertensive disorders of pregnancy (147)	18,724 women with singleton pregnancies who worked ≥ 1 day or night shift during the first 20 pregnancy weeks	Cumulated number and duration of night shifts, consecutive night shifts and quick returns during the first 20 pregnancy weeks	Age, BMI, parity, smoking, SES, sick leave three months prior to pregnancy	Hypertensive disorders of pregnancy	Logistic regression with comparisons of night versus day work and within-night work comparisons
II – Night work and sick leave during pregnancy (under peer-review)	9,799 women with both ≥ 1 day shift, ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks	Night shifts of different duration	None as the workers were their own control	Sick leave within 24 hours after a shift	Fixed effects of night versus day shifts in within-worker comparisons
III – Night work and severe postpartum depression (under peer-review)	19,382 women with singleton pregnancies who worked ≥ 1 day or night shift during the first 32 pregnancy weeks	Cumulated number and duration of night shifts, consecutive night shifts and quick returns during the first 32 pregnancy weeks	Age, BMI, parity, SES, sick leave three months prior to pregnancy, prior diagnosed severe depression	Severe postpartum depression	Logistic regression with comparisons of night versus day work and within-night work comparisons

7. Main results

In this section the main results of this thesis are presented. For a more detailed description along with further results see papers I-III in the appendix.

7.1 Cohort's demographic and working time characteristics

There were 9,642 day workers (at least one day shift and no night, evening or early morning shift during the first 32 pregnancy weeks) and 15,367 night workers (those who worked at least one night shift during the first 32 pregnancy weeks) in the whole cohort for the period 2007-2015. Night workers were primarily nurses (64%) and physicians (17%), while most of day workers were medical secretaries (18%), nurses (15%) and physiotherapists (14%). Both groups had similar age (mean 32.3 and 31.2 years, respectively) and BMI (both mean 23.9 kg/m^2). Night workers had a higher proportion of first time pregnancies (41%) than day workers (33%). Day workers had a higher proportion of low SES (18%) and smoking (3%) than night workers (6% and 2%, respectively) – see table 1 in paper III in the appendix. We had a high completeness of data with missing values for BMI, parity, smoking and SES representing only 4%, 1%, 2% and 0.7% respectively. There was no missing age.

The distribution of the different dimensions of night work throughout pregnancy, i.e. during the first 32 pregnancy weeks, was as follows:

➢ 8% of night workers had on average > 1 night shift per week;

➢ 39% of night workers had at least one night shift of > 12 hours;

➢ 18% of night workers had > 3 consecutive night shifts;

➢ 70% of night workers had at least one quick return; and

➢ 93% of night workers had at least one quick return after a night shift.

It is, however, important to keep in mind that these proportions were higher in the first half of the pregnancy. For instance, the proportion of workers having > 1 night shift per week was 18% in the 1st trimester, 13% in the 2nd trimester, and 4% in the 3rd trimester.

We observed considerable differences in the organization of night shifts between nurses and physicians (Table 2), reflecting their different collective agreements in Denmark (135-137). Nurses had higher proportion of night work, and had on average more evening shifts, more night shifts lasting ≤ 12 hours, more consecutive night shifts and more quick returns. Physicians had almost exclusively night shifts of > 12 hours and had no spells of > 3 consecutive night shifts at all. On the other hand, nurses had fewer weekly working hours compared to physicians both among day and night workers. Regarding their demographic characteristics, nurses were slightly younger (mean age of 31 vs. 33 years), had higher BMI (mean of 24.0 vs. 22.5 kg/m^2) and had higher proportion of smoking during pregnancy (2% vs. 0.2%) compared to physicians.

Table 2 – Working time characteristics during the first 32 weeks of 14,687 singleton pregnancies of nurses and physicians at public hospitals in Denmark, 2007-2015.

	Nurses (N= 11,289)				Physicians (N= 3,398)			
	N	%	Mean	SD	N	%	Mean	SD
Day workers[a]	1,447	13			744	22		
Day shifts			95.8	30.0			116.3	32.8
Weekly working hours[b]			22.2	7.2			26.8	7.7
Night workers[c]	9,842	87			2,654	78		
Day shifts			56.5	23.0			83.3	24.4
Early morning shifts			0,01	0,2			0.01	0.1
Evening shifts			16.2	14.3			2.1	4.5
Night shifts - total			14.8	13.0			13.8	7.7
Night shifts of ≤ 8 hours			7.3	10.7			0.01	0.1
Night shifts of > 8-12 hours			6.3	10.3			0.1	0.8
Night shifts of > 12 hours			1.2	3.9			13.7	7.7
Total number of consecutive night shifts when having only spells of 2-3 shifts			5.7	4.7			1.5	1.5
Total number of consecutive night shifts when having at least one spell of > 3 shifts			17.0	10.3			0	0
Quick returns[d]			3.7	3.9			0.9	2.8
Quick returns after a night shift[e]			8.5	8.7			6.5	4.3
Weekly working hours			22.5	6.3			29.2	6.3

[a] At least one day shift and no night, evening or early morning shift
[b] Paid and unpaid leave excluded
[c] At least one night shift
[d] interval of < 11 hours between any type of shifts
[e] interval of < 28 hours between a night shift and the next shift

7.2 Study I – Night work and hypertensive disorders of pregnancy

The prevalence of HDP in our cohort was 3.7%, which was lower than the prevalence observed in the general Danish population of around 6% (67).

We found an increased risk of HDP among women who worked > 3 consecutive night shifts during the first 20 pregnancy weeks (OR 1.41, 95% CI 1.01-1.98) compared to women who worked ≤ 3 consecutive night shifts – see figure 5. The prevalence of HDP in the reference group was 3,3 cases per 100 pregnant workers. The relative increase in risk of 41% corresponded to 1,4 (95% CI 0.1-3.2) extra cases of HDP per 100 pregnant workers with > 3 consecutive night shifts. We also observed a statistically significant trend of increasing risk of HDP with increasing number of quick returns after night shifts in within-night work comparisons (OR 1.28, 95% CI 0.77-1.95 for ≥ 5 quick returns after night shift). Comparisons with day workers revealed slightly increased risks, however not statistically significant (Figure 5).
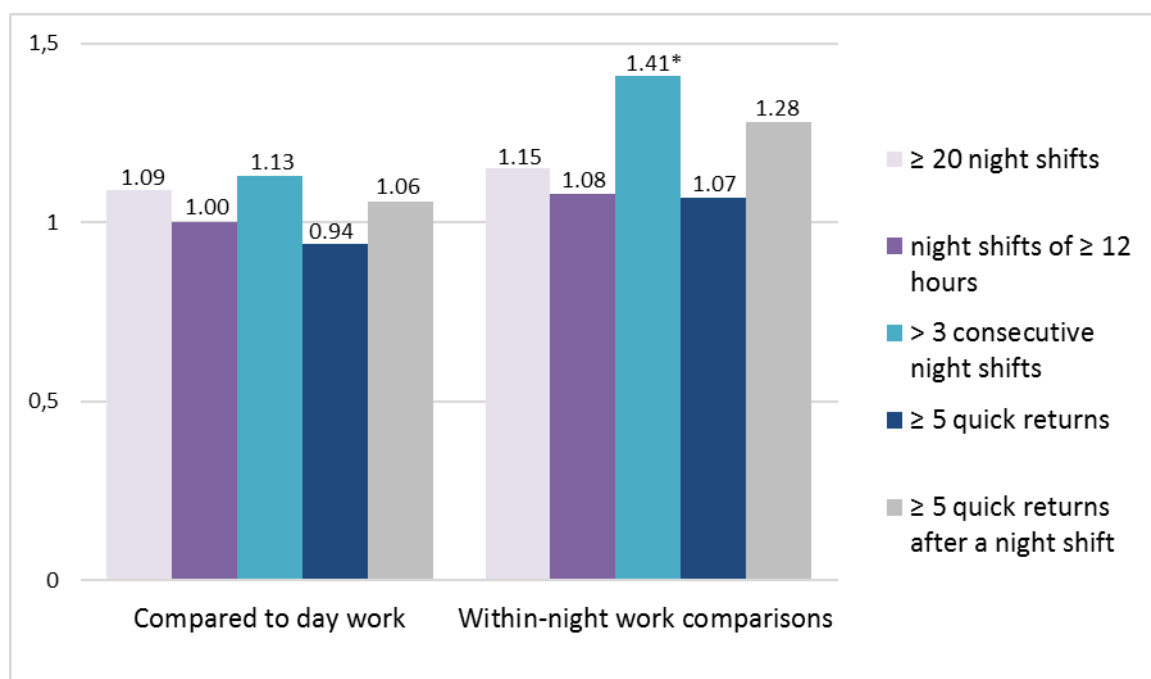
Figure 5 – Odds ratio of hypertensive disorders of pregnancy by different dimensions of night work during the first 20 pregnancy weeks among 18,724 Danish hospital employees, 2007-2013. The analyses were adjusted for age, body mass index, smoking, parity, socioeconomic status and sick leave three months prior to pregnancy. (* significance with level of 0.05)

Analyses stratified by BMI revealed that obese women (pre-pregnancy BMI ≥ 30 kg/m²) who worked at night had a 4- to 5-fold increased risk of HDP compared to day workers (Figure 6). This relative risk increase corresponded to 2.7 (95% CI 0.2-10.2) extra cases per 100 women who worked ≥ 1 night shift per week on average; 3.6 (95% CI 0.7-11.0) extra cases per 100 women who worked night shifts of ≥ 12 hours; 4.3 (95% CI 1.0-13.2) extra cases per 100 women who worked > 3 consecutive night shifts; 3.6 (95% CI 0.8-11.4) extra cases per 100 women who had ≥ 5 quick returns after night shifts during the first 20 pregnancy weeks. Due to low power we were not able to perform within-night work comparisons among obese women. Neither age nor SES modified the effect of night work on the risk of HDP.
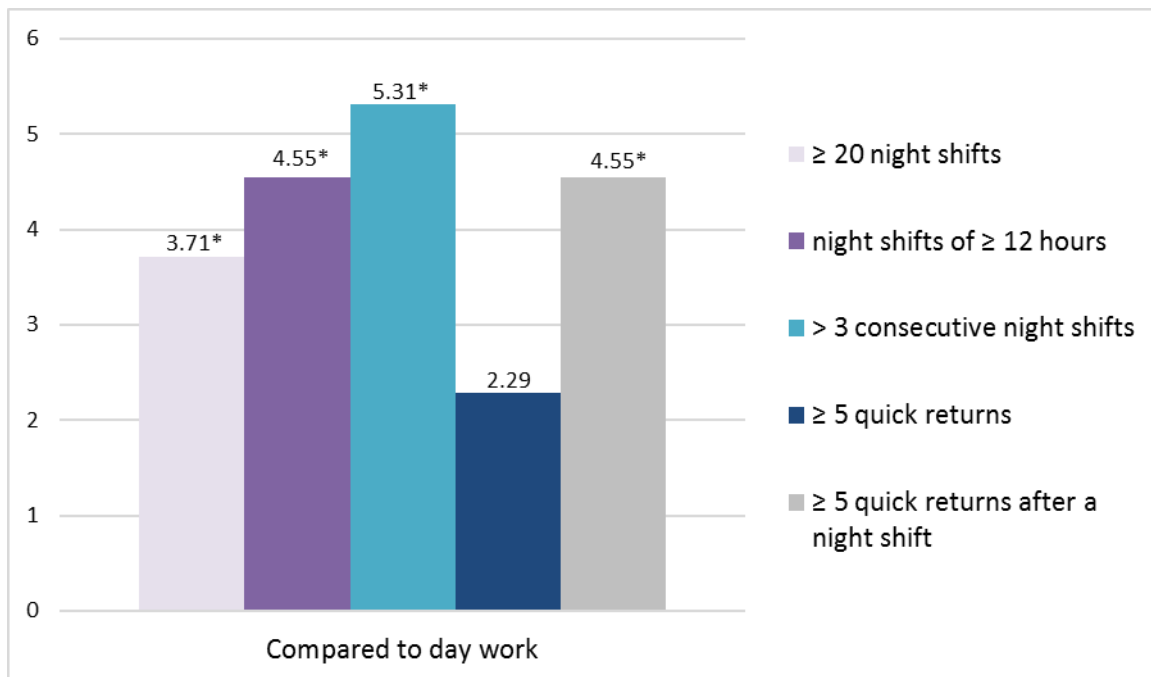
Figure 6 – Odds ratio of hypertensive disorders of pregnancy by different dimensions of night work compared to day work during the first 20 pregnancy weeks among 1,588 Danish hospital employees with body mass index ≥ 30 kg/m², 2007-2015. The analyses were adjusted for age, smoking, parity, socioeconomic status and sick leave three months prior to pregnancy. (* significance with level of 0.05)

We did not observe an increased risk of HDP among women who worked ≥ 1 night shift per week on average during the first 20 pregnancy weeks compared with day workers, as far as they did not have > 3 consecutive night shifts or were obese.

The main results were consistent in sensitivity analyses restricted to first time pregnancies, or with preeclampsia as the outcome, or restricted to the 1st trimester as the exposure time, although with slight attenuation of the estimates. Further adjustment for number of night shifts in analyses of long and consecutive night shifts, and quick returns did not substantially change the results.

We did not find any suggestion of the healthy worker effect as women who had night shifts during the 1st but not during the 2nd or 3rd trimester (N=1,762 corresponding to 17% of night workers during the 1st trimester) did not have increased risk of HDP compared to women who worked night shifts in all trimesters (adjusted OR 1.03, 95% CI 0.73-1.42).

7.3 Study II – Night work and sick leave during pregnancy

The study cohort consisted of 9,799 pregnant women, who had both ≥ 1 day shift, ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks. Regarding their total days of sick leave in this period, around 52% had up to 14 days; 13% had 15-28 days and 35% had > 28 days. This distribution was similar to the one observed among 20,912 pregnant women from the same source population with ≥ 1 shift of any type during the first 32 pregnancy weeks.

We observed an increased risk of sick leave of any duration starting within 24 hours after night versus day shifts in all pregnancy trimesters (OR 1.28, 95% CI 1.19-1.37 in the 1st trimester; OR 1.27, 95% CI 1.17-1.39 in the 2nd trimester; and OR 1.13, 95% CI 0.96-1.33 in the 3rd trimester). This risk increasement was driven by long night shifts (> 12 hours) both among nurses and physicians as shown in figure 7 (see table 3 in paper II in the Appendix for the results for night shifts lasting ≤ 8 and > 8-12 hours). The overall increased risk for long night shifts for the whole cohort was 55% (OR 1.55, 95% CI 1.43-1.69), where long shifts represented 99% of all night shifts among physicians, and only 7% among nurses. The overall increased risk during the first 32 pregnancy weeks for all night shifts was 23% (OR 1.23, 95% CI 1.17-1.29).

In addition to occupation, age also modified the effect of night work on the risk of sick leave with the highest estimates found among women older than 35 years (OR 1.42, 95% CI 1.24-1.63). The main results were slightly attenuated in sensitivity analyses restricted to first time pregnancies or using both sick leave and pregnancy leave as the outcome.
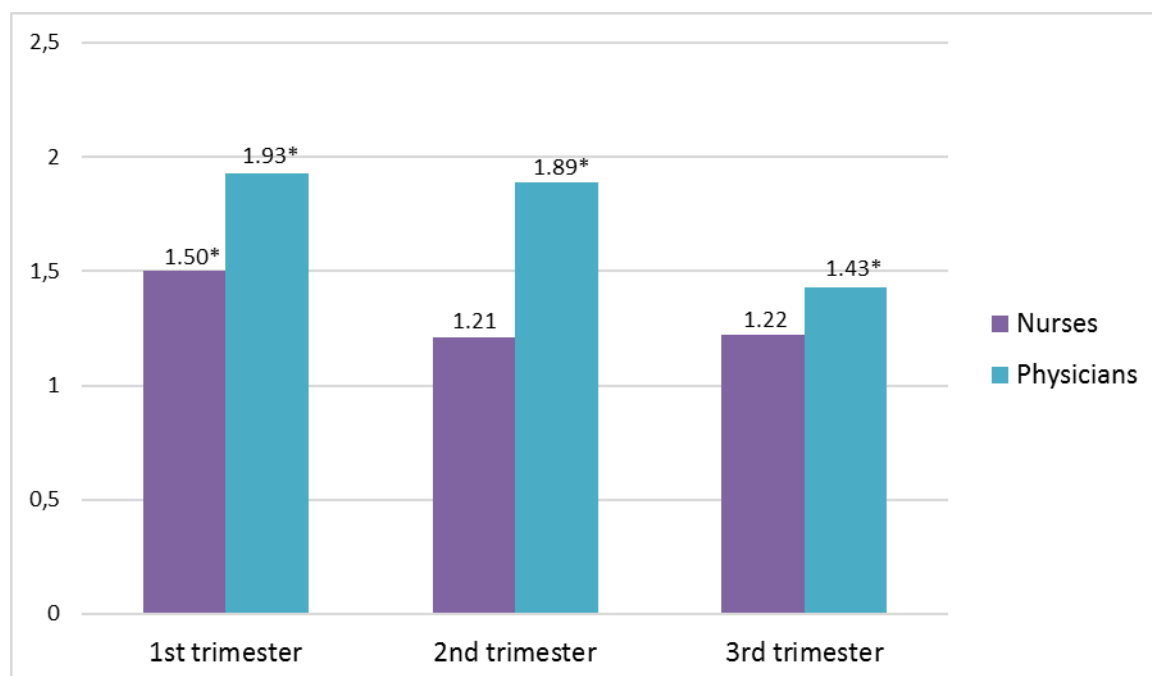
Figure 7 – Odds ratio of sick leave starting within 24 hours after night shifts longer than 12 hours versus day shifts during the first 32 pregnancy weeks stratified by pregnancy trimester with the participants as their own controls (fixed effects logistic regression) among 6,487 nurses and physicians at Danish public hospitals, 2007-2015. (*significance level of 0.05)

7.4 Study III – Night work and severe postpartum depression

The study cohort consisted of 25,009 singleton pregnancies from 19,382 women. We observed a prevalence of severe PPD of 0.3% (N=80 cases), which is in line with prior studies using information from Danish national registries (148). As expected, most of the cases of severe PPD (20%) had a prior diagnose of severe depression, in contrast to women who did not develop severe PPD (2%).

We did not observe an increased risk of severe PPD in relation to any of the dimensions of night work studied (Figure 8).
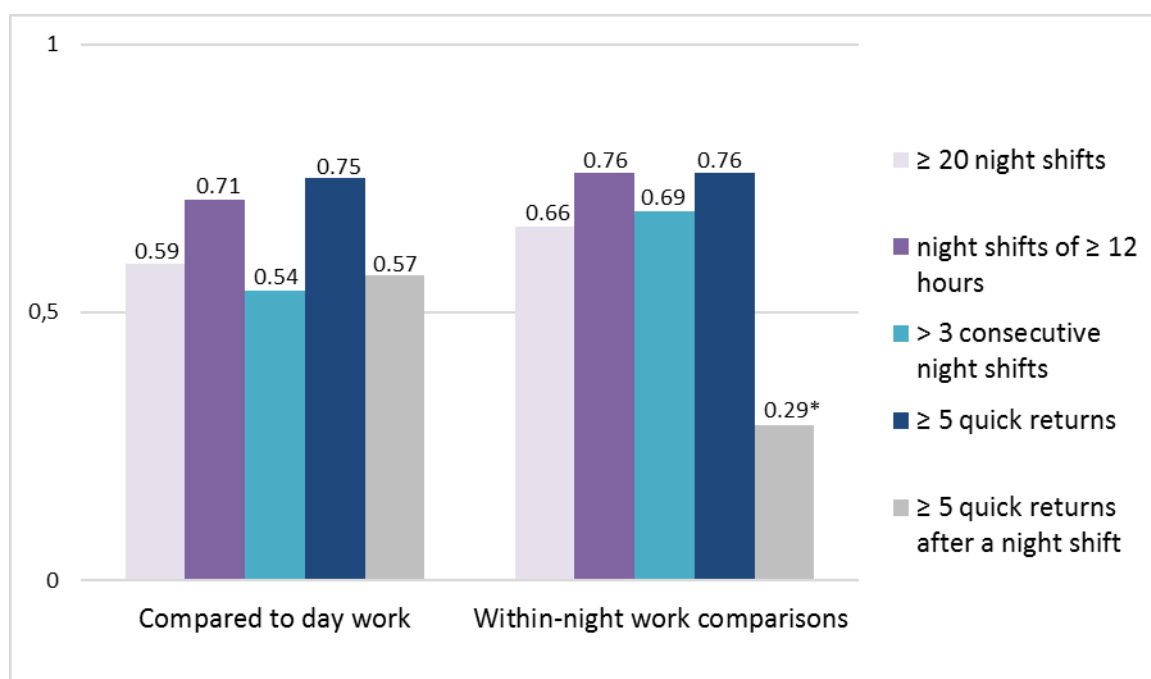
Figure 8 – Odds ratio of severe postpartum depression by different dimensions of night work during the first 32 pregnancy weeks among 19,382 Danish hospital employees, 2007-2015. The analyses were adjusted for age, body mass index, parity, socioeconomic status and sick leave three months prior to pregnancy and prior diagnosed severe depression. (*significance level of 0.05)

Within-night work sensitivity analysis were performed to investigate the potential effect of healthy worker survivor bias. We found that women who stopped working night shifts after the 1st trimester (N=3,094 corresponding to 22% of night workers in the 1st trimester) had an increased risk of severe PPD (OR 2.08, 95% CI 1.09-4.00) compared to women who worked night shifts throughout pregnancy. This risk was not increased (OR 0.79, 95% CI 0.35-1.80) among women who stopped working night shifts after the 2nd pregnancy trimester (N=5,325). These findings suggest the presence of healthy worker survivor bias, where women susceptible to severe PPD stopped working night shifts after the 1st pregnancy trimester.

Sensitivity analyses restricted to nulliparous women (N=9,332) and to pregnancies without prior diagnosed severe depression (N=24, 582) did not substantially change the results. Analysis restricted to nurses (N=11 298) revealed a tendency of increased risk of PPD among women in the lowest categories of exposure compared with day work, however, none of the results were statistically significant (Table 3).

Table 3 - Risk of severe postpartum depression by different dimensions of night work during the first 32 pregnancy weeks among 11,298 nurses employed at Danish public hospitals, 2007-2015.

Dimension of night work	Adjusted[a] odds ratio	95% confidence interval
Day work	1.00	Reference
1-8 night shifts	1.49	0.44-5.04
≥ 9 night shifts	0.71	0.20-2.48
Only night shifts of ≤ 8 hours	1.12	0.31-4.05
At least one night shift of > 12 hours	1.06	0.27-4.18
No consecutive night shifts	1.27	0.31-5.10
2-3 consecutive night shifts	0.96	0.28-3.27
> 3 consecutive night shifts	1.05	0.28-3.99
No quick returns	1.56	0.42-5.82
≥ 9 quick returns	0.84	0.25-2.75
1-8 quick returns	1.15	0.23-5.75
No quick returns after night shifts	1.25	0.22-6.97
1-8 quick returns after night shifts	1.16	0.35-3.89
≥ 9 quick returns after night shifts	0.75	0.19-2.87

[a] adjusted for age, body mass index, parity, socioeconomic status and sick leave three months prior to pregnancy and prior diagnosed severe depression

8. Discussion

In this section, the main findings along with methodological aspects from the three studies are discussed with reference to relevant previous studies.

8.1 Key findings

Study I – Hypertensive disorders of pregnancy

Consecutive night shifts

To the best of our knowledge, this is the first study to investigate the association of HDP with different dimensions of night work using nationwide information from hospital registries and payroll data.

We found that working > 3 consecutive night shifts during the first 20 pregnancy weeks increased the risk of HDP by 40% compared to having night work but without consecutive night shifts. Findings from within-night workers comparisons support a potential causal association, as the groups are more homogeneous than in comparisons of night versus day workers.

Consecutive night shifts have been associated with hormonal changes affecting circadian regulation in a dose-effect pattern, especially after ≥ 3 night shifts in a roll, but substantial changes were also seen after 1-2 consecutive night shifts (149-151). The fact that adjustment for number of night shifts did not change the results confirm that the effect is due to the sequences of shifts in a roll rather than a high total number of night shifts. This is similarly shown by studies of breast cancer that highlighted the importance of considering the intensity of night work – expressed by consecutive night shifts – rather than the crude assessment of night work as yes/no or number of shifts in relation to hormonal and chromosomal changes associated with circadian disruption (152, 153). It is, however, important to keep in mind that the different dimensions of night work are correlated. For example, consecutive night shifts results automatically in quick returns after night shifts according to our definition of shift interval of < 28 hours. This is supported by our findings of a statistically significant trend of increasing risk of HDP with increasing number of quick returns after night shifts. However, the contrary is not always true, as quick returns after night shifts do not necessarily occur between two night shifts. Nevertheless, the results from these two dimensions of night work support the recommendation from previous studies of at least two days off following a night shift to allow adequate circadian readjustment (150, 154, 155). This is especially important for our cohort of hospital employees, where most have irregular shift schedules.

The combined effect of night work and obesity

Among obese women all dimensions of night work were consistently associated with a 4- to 5-fold increased risk of HDP compared to day workers. These substantially increased risks support the evidence of night work as a risk factor for HDP, as obesity, both in relation to pre-pregnancy BMI and weight gain during pregnancy, is one of the strongest predictors of HDP (156-158). It is worth noticing that, among obese women, we neither find a higher proportion of workers with fixed night shifts nor a gradient of higher BMI among night workers.

Comparisons with day work

We did not observe an increased risk of HDP among women who worked > 1 night shift per week during the first 20 pregnancy weeks compared with day workers, as far as they did not have > 3 consecutive night shifts or were obese. A possible explanation for that might be differences of work content, such as physical and psychosocial stressors between day and night work. In addition, even though we did not find evidence of healthy worker survivor effect, where susceptible women stop working night shifts during pregnancy, the possibility of the healthy worker hire effect remained. The design of our study was not appropriate to investigate this selection bias, where women with health problems in general tend to choose day work already prior to pregnancy.

Our findings of no effect of night work in the risk of HDP in comparisons with day work are in line with four out of five previous studies. These studies had, however, crude assessment of work schedules and did not perform within-night work comparisons.

The cut-offs we applied are based on prior studies using payroll data, but they are not strictly based on biological plausibility. However, the cut-off of > 1 night shift per pregnancy week seems to be consistent with increased risks of negative health effects during pregnancy. For instance, in a recent study of over 22,000 women from the same source population we found that > 1 night shift per week increased the risk of miscarriage by 30% (hazard ratio 1.32, 95% CI 1.07-1.62) (*Begtrup LM et al. (2018) Night work and miscarriage: a Danish nationwide register-based cohort study. Submitted to the Journal of Occupational and Environmental Medicine*).

Study II – Sick leave

Long night shifts

In this first study of the acute effect of night work on the risk of sick leave during pregnancy using the participants as their own controls, we found that long night shifts increased the risk of sick leave within a 24-hours period by over 50%. This risk was increased in all pregnancy trimesters. Hence, even women who endured night shifts until the end of the pregnancy were at higher risk of sick leave following night shifts compared to day shifts.

Possible role of fatigue and lack of recovery

This acute effect of night work on the risk of sick leave starting shortly after the shift is most probably driven by fatigue and lack of recovery added to the effects of disturbed sleep and fatigue physiologically imposed by pregnancy.

The combination of long night shifts and increased work load is a possible aggravating factor for the increase in sick leave rates after night shifts. This hypothesis is supported by the differences in the organization of night shifts we observed among nurses and physicians. Nurses had primarily 3-shift schedules, i.e. shifts lasting around 8 hours within a 24-hour period. So, long night shifts among nurses occurred in general when they had two or more shifts in a row. In a hospital setting, this usually happens when there is increased workload, such as sick leave among employees or overcrowded hospital beds. Physicians had primarily long night shifts. Even though they had more on-call shifts than nurses, emergency duties across departments limit in praxis their possibility of rest during the shift.

It has been shown that 12-hour shifts in general (not only night shifts) are associated with increased fatigue despite their positive effects on job satisfaction resulting from compensatory days off (111). Actually, only slightly extended shifts of 9 hours among nurses were found associated with increased fatigue, more health complaints, and less satisfaction compared to 8-hours shifts (111).

Besides confirming the findings from previous studies of increased sick leave during pregnancy among night workers, our results add to the understanding of possible reasons for that. As argued above, our study indicates that fatigue and lack of recovery contribute substantially to this risk.

Short shift intervals

Even though the design of this study was not appropriate to investigate the effect of consecutive night shifts and quick returns separately, the risk period of 24 hours following a night shift was comprised within the definition of quick return after night shifts (shift interval of < 28 hours). In another words, each occurrence of sick leave following a night shift corresponded to calling in sick from a potential quick return after a night shift, which might as well be a consecutive night shift. Accordingly, both consecutive night shifts, quick returns (shift interval of < 11 hours) and quick returns after night shifts were shown to increase fatigue and sleep disturbance among nurses and physicians (159-162), and also among a representative national sample of Swedish workers (93).

Age

Our findings of higher risk of sick leave following night shifts of women older than 35 years is in line with the higher risk of pregnancy complications among these women (139, 163).

Study III – Severe postpartum depression

We found no association of PPD requiring hospital treatment with any of the dimensions of night work investigated. To our knowledge, this is the first study of severe PPD in relation to night work during pregnancy.

Possible role of the healthy worker survivor effect

We found that 22% of the night workers in the 1st trimester had work schedules without night shifts latter in pregnancy. These women had a 2-fold increased risk of severe PPD compared to those who continued working night shifts in the 2nd and 3rd trimester. These findings indicate the presence of a healthy worker survivor effect, which might have contributed to underestimation of the effect of night work in the overall analyses. We did not have information on the reason for changing work schedules among these women, but we hypothesize that they were somehow more susceptible to developing severe PPD. Conversely, women who worked night shifts throughout pregnancy, and had therefore the highest exposure to night work, had probably a relatively higher health status. As women with predisposition for depression seem to be more susceptible to both hormonal changes and sleep disturbances during pregnancy, they might as well be more susceptible to circadian disruption induced by night work (62, 63, 123-125, 164-166).

It is possible that the healthy worker survivor effect is also present within night workers. This is supported in our study by findings of a tendency of elevated risks of PPD in the lowest categories of exposure to night work as shown in table 3. This might reflect that workers who take compulsory night work despite of a poorer health status or lack of adaptation to night work, might avoid having consecutive or long shifts, or quick returns. However, this interpretation requires caution, as none of the results were statistically significant, and the statistical method applied can only suggest the presence of such effect.

One possible reason for the association between selection out of nigh work and severe PPD, is that the worsening of depressive symptoms in relation to night work is more easily recognizable than other effects associated with night work, such as increased blood pressure. Depressive symptoms have indeed been associated with increased risk of changing from shift to day work (OR 1.98, 95% CI 1.13-3.47) in a cohort of nearly 10,000 workers from the Maastricht Cohort (blue- and white-collar workers from 45 companies and organizations in the Netherlands) (167). Another prospective study based on the same cohort investigated changes in mental health as a predictor of changes in work schedules and occupational mobility (168). They found a tendency to change from shift to day work among workers who reported prolonged fatigue (OR 3.44, 95% CI 1.42-8.38), need for recovery (OR 1.36, 95% CI 0.34-5.45), and psychological distress, measured by the 12-item version of the General Health Questionnaire (OR 2.26, 95% CI 0.84-6.04).

Previous longitudinal studies, that similarly to our study investigated the association between night work and depression among hospital employees found conflicting results – four found positive association (162, 169-171) and two found no association (161, 172). Only two studies accounted for changes of work schedules. An interesting study of nearly 50,000 Finnish healthcare employees investigated the association of mobility in and out of night

work with the risk of common mental disorders (CMD), defined as sick leave due to any mental disorder or antidepressant purchase, in a non-randomized pseudo trial design (171). In analysis not accounting for changes of work schedules they found no association between night work and CMD (OR 1.03, 95% CI 0.82-1.30). However, when accounting for such changes, they found that 1) changing from non-night to night work increased the risk of CMD (OR 1.25, 95% CI 1.03-1.52); 2) night workers who developed CMD had a 68% increased odds of moving back to non-night work; and 3) night workers with CMD had higher odds of recovery when changing to non-night work (OR 1.99, 95% CI 1.20-3.28). Similarly, a 2-year follow-up study of over 600 Norwegian nurses found that anxiety and depressive symptoms improved after changing from night to day work compared to day workers (170).

As pointed out by Chowdhury and colleagues (129), the extent of the healthy worker effect is not constant over time and varies across age groups, race, SES and occupations. Therefore, it is not surprising that we found a strong indication of the healthy worker survivor effect in study III in contrast to the study I, despite using the same source population. We neither found indication of the healthy worker survivor effect in another study from the same source population on the risk of preterm birth in relation to night work *(Specht IO et al. (2018) Night work during pregnancy and preterm birth – A large register-based cohort study. Submitted to Plos One)*.

8.2 Methodological aspects

Internal validity

Our studies have several important methodological strengths, that adds to high internal validity:

➢ Nationwide study sample from all public hospital employees in Denmark, thus providing a sample size that allowed detailed analyses of different work schedules and timing in pregnancy;

➢ Detailed, day-to-day information on working hours based on payroll data;

➢ Within-night work comparisons;

➢ Prospective design;

➢ Medically diagnosed disorders based on National hospital registries, instead of self-reported symptoms;

➢ Pregnancy period-specific effects, which allowed us to account for changes of work schedules during the pregnancy period.

Still, potential confounding and bias needs attention.

Confounding

In study I and III, comparisons among night workers only render findings less susceptible to healthy worker effect and to unmeasured confounding – both related to work content and to demographic characteristics.

Within-night work comparisons accounted to some extent for differences of work content, such as job tasks and workload. However, such differences might still have played a role across occupations, as the health effects of night work might act differently in combination with other exposures, such as physically demanding work, noise, and psychosocial factors (90, 112, 173, 174).

Furthermore, work content is a time-varying factor even for the same worker. This might have been a source of bias towards the null in study II, despite of the within-worker analyses, and in study III. The reason for the latter is that psychosocial factors might mediate some of the effect of night work on the risk of depression (126).

In study I, on HDP, we were able to control for the most important confounders, namely age, BMI, parity, smoking, SES and health status prior to pregnancy.

In study III, however, we lacked information on some relevant risk factors for PPD, such as family history of depressive disorders, social support, and adverse life events. On the other hand, we have no a priory evidence that link these factors to the exposure, and thus confounding is hypothetical.

Selection

The use of National register-based data made bias due to selection in and out of the cohort unlikely. The main reason for a participant to come out of the cohort was change of employment from public to private hospitals or to primary sector. Even in these cases, as most of the cohort were nurses or physicians, they would still be part of the cohort in the first years of their career until the conclusion of their education or specialization.

We had complete data on sick leave for all the workers in the cohort, in contrast to several prior studies, which were not able to account for sick leave.

Even though we explored the presence of the healthy worker survivor effect in our cohort, the statistical methods we applied were not adequate to account for such an effect. Furthermore, as previously mentioned, we did not investigate the potential presence of the healthy worker hire effect.

Adaptation to night work

Mechanisms of selection in and out of night work are complex and driven, at least partially, by several factors involved in adaptation to night work, such as chronotype and work-life balance (175-178). Adaption to night work can refer to the physiological alignment of a person's circadian rhythm, or to a person's satisfaction with her/his work-life balance.

Researchers might want to investigate these aspects separately, but they are in reality tightly correlated.

It is not simple to evaluate how the results of our studies would be affected by accounting for personal preference and adaptation. In one hand, the negative effects of night work on health would, in theory, be more pronounced among those who do not adapt physiologically to night work. On the other hand, the psychosocial benefits of experiencing work-life balance might overcome the physiological changes of working against ones' biological clock. Whether this might be the case depending on the health outcome of interest. Nevertheless, psychological resilience and coping seem to be strongly related with psychological well-being (179). In our cohort of hospital employees, many workers have compulsory night work, where self-selection out of night work might not be possible for several reasons.

Considering that evening chronotype has been associated with the development and severity of depressive disorders (180), the lack of information on chronotype from the participants in study III might have biased the results towards the null.

Misclassification

Misclassification regarding exposure to night work is virtually zero, as payroll data are the base to salary calculations. However, some underestimation of the duration of shifts is expected in cases of unregistered extra working hours (130). This is though not expected to have affected the analysis of the individual night shifts substantially, but it could be the case, for instance, in analyses of total working hours per week.

Non-differential misclassification of the outcome might have biased the results towards the null both in study I and III. As we used hospital registries to identify cases of HDP and PPD, mild cases treated in the primary sector were not included. This is probably one of the reasons for the lower prevalence of HDP in our cohort compared to the Danish background population. Another reason could be the misclassification of severe cases of HDP. The study of Luef and colleagues on validation of hospital discharge diagnoses for HDP in Denmark (133) showed sensitivity of 56% and 19% for cases of preeclampsia and severe preeclampsia, respectively. Even though the prevalence of severe PPD in our study corresponded to the prevalence reported by previous population-based Danish studies (148), the relatively few cases in our cohort challenged the statistical power of the study.

On the other hand, the use of hospital registries for the outcome assessment ensured high specificity of 99% for cases of HDP (133) and 83% for cases of severe depressive episodes (181).

Competing risk

Previous studies have shown that fixed night work is a risk factor for miscarriage (56, 59). These findings were confirmed in our cohort of night workers having irregular shift work, where we found that > 1 night shift per week increased the risk of miscarriage by 30%, especially after pregnancy week eight (*Begtrup LM et al. (2018) Night work and miscarriage: a Danish nationwide register-based cohort study. Submitted to the Journal of Occupational and Environmental Medicine)*. As a result, miscarriage can be responsible for reduction in the risk time for outcomes depending on cumulative exposure assessment. Further, as this reduction of risk time is not random, as it happens especially among women who work at night, miscarriage is a competing risk for the outcome of study I and III. Consequently, the results from these studies might be underestimated.

External validity

The external validity, or generalizability, of a study express the possibility of applying its results to other populations. We believe that our results might apply to other populations of pregnant workers as far as they have similar work schedules of irregular shift work including night shifts. It is though important to notice that we had relatively few fixed night workers, and we performed comparisons of night versus day work, so we did not include workers with other schedules such as fixed evening work.

Also worth of noticing is the relatively lower prevalence of some risk factors associated with pregnancy complications in our cohort compared to the Danish background population, such as smoking (3% versus 12%) (182) and overweight (19% versus 46%) (183). It is therefore possible that the extent of the negative effects of night work might be larger in other populations with higher prevalence of such risk factors. In addition, higher risks might also be observed in occupations combining night work with other exposures, such as physically demanding activities and noise, which is the case in the industrial sector.

9. Conclusion

The primary aims of the **PREGNIGHT** project were 1) to investigate the risk of potentially severe medically diagnosed disorders and sick leave in relation to night work during pregnancy, and 2) to identify ways of organizing night work during pregnancy that might reduce its potential negative health effects.

We found that night shifts during pregnancy, especially long or consecutive shifts, increased the risk of sick leave and hypertensive disorders of pregnancy by around 50% and 40%, respectively. The combined effect of obesity and night work increased the risk of HDP by 4-5-fold. We found no increased risk of severe PPD given the current mobility out of night work among hospital employees. These results were consistent across studies using different methods.

Our findings support the hypothesis that the health effects of night work are more related to the way night shifts are organized rather than the mere presence of night shifts.

Overall, if pregnant women work night shifts, adequate shift intervals along with reduction of their frequency and duration might reduce sick leave and HDP. Especial attention must be paid to women who do not adapt to night work and those with other risk factors for pregnancy complications.

10. Perspectives

10.1 Practical Implications

In Denmark, pregnant workers are not restrained from night work. Hereby, identification of potential negative health effects of night work is so far based on individual evaluation.

Our results raise considerations relevant for pregnant workers, employers, health professionals and decision makers in public health of whether and how to organize night work during pregnancy.

To place our results in a public health perspective let us consider the substantial risk increases we observed among obese pregnant women working at night. We found that 1,588 women were obese corresponding to 9% of the cohort in the study period of 2007-2013. Among them, 917 worked at night during the first 20 pregnancy weeks. So, the 5-fold increased risk of HDP found among women who had > 3 consecutive night shifts corresponded to 4.3 extra cases per 100 women who had such work schedule, or 39.4 extra cases over a 7-year period (roughly 5.6 cases per year). For sick leave the risk increase observed corresponded to 1.5 extra days of sick leave per 100 long night shifts during the first 32 pregnancy weeks.

On the other hand, we found no increased risk of negative health effects among women who worked up to one night shift per week on average during pregnancy, as far as they did not have > 3 consecutive night shifts or were obese. If this result was to be false, the risks are expected to be rather small.

It is estimated that around 10% and 14% of the female workers in Denmark and Europe, respectively, work at night. Restraining pregnant women from work at night would therefore have considerable socioeconomic impact. Weighting such socioeconomic and public health costs is a challenge for decision makers. Nevertheless, all potentially modifiable risk factors for reproductive hazards must be taken into account by health care professionals who advise workers and employers on health risks of night work during pregnancy.

10.2 Future research

We suggest future researchers in this field to apply clear definitions and different dimensions of shift work through detailed and validated information on working hours throughout or, at least, during different time periods of pregnancy. Despite substantial methodological strengths of our studies, replication of the results by other research groups is needed.

Possible next steps to corroborate our findings could be:

➢ intervention studies of job adjustment during pregnancy aiming at specific dimensions of night work, which would be the ultimate proof of causality;

➢ studies combining payroll data and factors related to adaptation to night work, such as chronotype and work-life balance;

➢ evaluation of whether and how pregnancy complications affect work schedules in subsequent pregnancies;

➢ studies applying epidemiological and statistical methods that account for the healthy worker survivor and hire effect.

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12. Appendix

Papers I-III

Paper I (published)

Night work and hypertensive disorders of pregnancy: a national register-based cohort study

Hammer P, Flachs E, Specht I, Pinborg A, Petersen S, Larsen A, Hougaard K, Hansen J, Hansen Å, Kolstad H, Garde A, Bonde JP.

Original article

Night work and hypertensive disorders of pregnancy: a national register-based cohort study

by Hammer P, Flachs E, Specht I, Pinborg A, Petersen S, Larsen A, Hougaard K, Hansen J, Hansen Å, Kolstad H, Garde A, Bonde JP

In this nationwide study, we investigated the association of hypertensive disorders of pregnancy with different dimensions of night work objectively assessed through payroll data. Our results indicate that working consecutive night shifts during the first 20 pregnancy weeks increases the risk of hypertensive disorders by 41%, which may be considered when providing recommendations on organization of night work during pregnancy.

Affiliation: Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, Bispebjerg Bakke 23, indgang 20F, 2400 Copenhagen, Denmark. paulahammer@dadlnet.dk

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/29669140

Additional material
Please note that there is additional material available belonging to this article on the *Scandinavian Journal of Work, Environment & Health* -website.

*O*riginal article

Night work and hypertensive disorders of pregnancy: a national register-based cohort study

by Paula Hammer, MD,[1] Esben Flachs, MSc, PhD,[1] Ina Specht, MSc, PhD,[2] Anja Pinborg, MD, PhD,[3] Sesilje Petersen, MSc, PhD,[1] Ann Larsen, MSc, PhD,[4] Karin Hougaard, MSc, PhD,[4, 5] Johnni Hansen, MSc, PhD,[6] Åse Hansen, MSc, PhD,[4, 5] Henrik Kolstad, PhD,[7] Anne Garde, PhD,[4, 5] Jens Peter Bonde, MD, PhD [1, 5]

Objective The aim of this study was to investigate whether night work expressed by number and duration of night shifts, number of consecutive night shifts, and number of quick returns during the first 20 weeks of pregnancy is a risk factor for hypertensive disorders of pregnancy (HDP).

Methods The study population comprised Danish workers in public administration and hospitals who gave birth between 2007 and 2013. Exposure was assessed objectively through payroll data. Information on the outcome was retrieved from the National Patient Register. We performed logistic regression on the risk for HDP according to night work adjusted for age, body mass index (BMI), parity, socioeconomic status, and sickness absence prior to pregnancy.

Results Among 18 724 workers, 60% had at least one night shift during the first 20 weeks of pregnancy. The prevalence of HDP was 3.7%. Among night workers, the risk of HDP grew with increasing number of consecutive night shifts [odds ratio (OR) 1.41, 95% confidence interval (CI) 1.01–1.98) and of quick returns after night shifts (OR 1.28, 95% CI 0.87–1.95). Among obese women (body mass index ≥30 kg/m²), those who worked long night shifts and longer spells of consecutive night shifts, and had the highest number of quick returns after night shifts, had a 4–5 fold increased risk of HDP compared to day workers.

Conclusion Working consecutive night shifts and quick returns after night shifts during the first 20 pregnancy weeks was associated with an increased risk of HDP, particularly among obese women.

Key terms circadian disruption; gestational hypertension; hypertension; payroll data; preeclampsia; shift work; shift worker; work schedule; working time.

Around 14% of the female European workers <50 years engage in night work (1). Several studies have investigated adverse pregnancy outcomes in relation to work schedules during pregnancy (2–6), but studies focusing on the pregnant women's health are sparse (7–9).

Hypertensive disorders of pregnancy (HDP) including preeclampsia and gestational hypertension occur in around 8% and 5% of pregnancies worldwide and in Denmark, respectively, and are a major cause of morbidity and mortality (10–12). It is suggested that the incidence of HDP has increased over time probably due to advanced maternal age and increased occurrence of obesity and diabetes in mothers (13, 14). The pathophysiology of HDP is not fully elucidated but seems to involve maternal, fetal and placental factors (14–19).

Night work, including both fixed night shifts and shift work, may influence the risk of HDP in several ways. Psychosocial factors related to night work, such as low job control and work-life conflict, have been associated with cardiovascular diseases including hypertension (20, 21). Another mechanism is through behavioral changes induced by night work affecting sleep, smoking

[1] Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, Copenhagen, Denmark.
[2] The Parker Institute, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark.
[3] Department of Obstetrics and Gynecology, Hvidovre University Hospital, Copenhagen, Denmark.
[4] National Research Centre for the Working Environment, Copenhagen, Denmark.
[5] University of Copenhagen, Department of Public Health, Copenhagen, Denmark.
[6] Danish Cancer Society Research Center, Copenhagen, Denmark.
[7] Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark.

Correspondence to: Paula EC Hammer, Bispebjerg Bakke 23, indgang 20F, 2400 Copenhagen, Denmark. [E-mail: paulahammer@dadlnet.dk]

habits, physical activity, diet and body mass (20, 22). Furthermore several physiological mechanisms including circadian disruption, hormonal changes, altered lipids and increased inflammation markers have been proposed linking night work with cardiovascular diseases (20, 22, 23). Melatonin, one of the main hormones affected by circadian disruption, is also produced in the placenta and plays a crucial role in maternal, fetal and placental physiology acting as an anti-inflammatory and immunomodulatory hormone, as well as a regulator of apoptosis (24–32). Furthermore the circadian oscillation of blood pressure is controlled in part by melatonin (33, 34). An altered circadian pattern of blood pressure has been reported in HDP, and as a result melatonin has been studied for its potential use in the treatment of preeclampsia (35, 36).

The few studies that have been conducted on the association between night and shift work with HDP revealed conflicting results (37–40). A major limitation of these studies is the crude assessment of work schedules. For instance in three (37, 38, 40) out of four studies it was not clear whether their definition of shift work included night shifts.

Payroll data provides accurate information on work schedules for a large population overcoming hereby the limitations related to exposure assessment in prior studies (41, 42).

The primary aim of this study was to investigate whether night work expressed by number and duration of night shifts, number of consecutive night shifts and number of quick returns during pregnancy is related to increased risk of HDP. We furthermore investigated whether age, body mass index (BMI) and socioeconomic status (SES) modified the effect of night work on the risk of HDP.

Methods

Design

We conducted a prospective register-based cohort study with information from three Danish national registries linked on individual level through the civil registration number given to all residents in Denmark since 1968.

The Danish Working Hour Database (DWHD), a national payroll database covering more than 250 000 employees in the Danish administrative regions including all hospital employees, provided the source population. It includes daily information on time of start and end of all workdays, sickness absence, paid and unpaid leave, occupation and place of employment from January 2007 to December 2015 (41, 43). Pregnancy information and covariates were identified from the Danish

Medical Birth Registry, which contains information from all home and hospital births in Denmark from 1973 onwards (44). Outcome variables were identified from the Danish National Patient Registry, which provides data on inpatients in Danish hospitals since 1977 and on outpatients since 1994 (45).

Study cohort

Women from DWHD who gave birth at least once between 2007 and 2013 were identified (N=42 485 women with 60 482 births). We excluded women ≤18 and ≥50 years (N=15), multiple pregnancies (N=2957), pregnancies conceived in 2006 (N=6403), and pregnancies from women without registrations in DWHD of any night or day shift during the first 20 pregnancy weeks (N=26 481). This was the exposure time because gestational hypertension is, by definition, diagnosed after 20 pregnancy weeks (14). To avoid clustering effects, each woman contributed with only one pregnancy, the first during the study period (N=5902 pregnancies excluded), leaving 18 724 women eligible for analyses (figure 1).

Exposure

Exposure definitions are in line with recent studies using payroll data (41, 46).

Shifts, including on-call shifts, lasting ≥3 hours were defined as day (start time after 06:00 and end time before 21:00 hours), evening (end time after 21:00 and before 02:00 hours), night (any start and end time including working hours between 23:00 and 06:00 hours) and early morning (start time between 03:00 and 06:00 hours).

A night worker was defined by working ≥1 night shift and a day worker by working ≥1 day shift but no night, evening or early morning shifts during the first 20 pregnancy weeks.

Consecutive night shifts. Categories of consecutive night shifts were 0 (only single night shifts), 2–3 (at least one spell of 2–3 consecutive night shifts and no spells of ≥4 consecutive night shifts), and ≥4 (at least one spell of ≥4 consecutive night shifts) during the first 20 pregnancy weeks.

Quick returns. We defined quick returns as intervals between shifts lasting <11 hours (47). Quick returns after night shifts were defined as a recovery period of <28 hours after a night shift (46). Categories of number of quick returns and quick returns after night shift were 0, 1–4 and ≥5 quick returns during the first 20 pregnancy weeks.

Duration of night shifts. Long night shift workers were defined by working ≥1 long night shift (≥12 hours) during the first 20 pregnancy weeks.

Figure 1. Flowchart for identification of the study population.
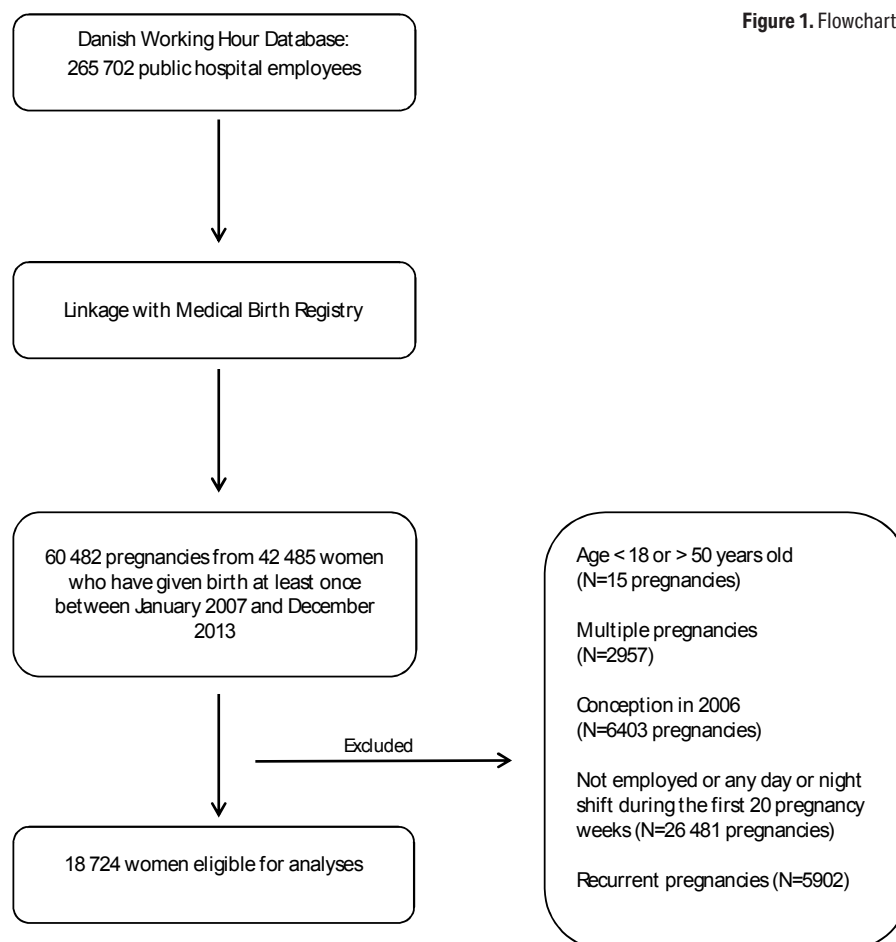
Number of night shifts. Number of night shifts was analyzed in categories of 1–19 or ≥20 (roughly corresponding to ≥1 night shift/week during the first 20 pregnancy weeks).

Covariates

Age (<30, 30–35, >35 years), BMI (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), parity (1, 2, ≥3) and smoking (nonsmoker, former smoker, smoker) registered by the midwife or family doctor at the first antenatal visit were retrieved from the Danish Medical Birth Registry. Classification of SES into high, low or medium was derived from Statistics Denmark. It was based on DISCO-88, the Danish version of the International Standard Classification of Occupations (ISCO-88) (48), in the calendar years 2007–2009, and DISCO-08, the Danish version of ISCO-08 (49), in the calendar years 2010–2013.

Sickness absence three months prior to pregnancy was expressed as the sum of all days registered with ≥3 hours of sickness absence in DWHD during this period. It was categorized as 0, <10 and ≥10 days.

Missing values for parity, smoking and SES represented only 1.4%, 2.9% and 0.2% respectively. Missing values for BMI (4.4%) were evenly distributed across exposure categories. Missing values of sickness absence three months prior to conception (7.9%) occurred when the woman's employment covered by DWHD had <3 months prior to conception.

Outcome

The outcome of HDP was defined by ICD-10 codes (50): hypertension (I10-15), gestational hypertension (O12, 13, 16) and pre-eclampsia and eclampsia (O14, 15).

Statistical analysis

We computed odds ratios (OR) with 95% confidence intervals (CI) for HDP according to different dimensions of night work during the first 20 weeks of pregnancy by logistic regression. Model 1 refers to crude analyses and model 2 is adjusted for age, BMI, parity, smoking, SES and sickness absence three months prior to pregnancy categorized as described above. Because of too few cases, it was not possible to adjust the analyses for cases of prior HDP (N=287), prior diabetes (N=17), and current

gestational diabetes (N=202). Model 3 is further adjusted for number of night shifts in the analyses of consecutive night shifts, quick returns and duration of night shifts.

In all analyses, except for interaction analyses, we made comparisons of night workers with day workers and comparisons within night workers. In the latter, night workers in the lowest category of exposure (1–19 night shifts, duration of night shift of <12 hours, night workers without consecutive night shifts and night workers without quick returns) were used as the reference group.

We investigated whether the association between night work and HDP was modified by age, BMI and SES by a likelihood ratio test comparing models with main effects only with models that in addition included an interaction term, ie, the product of the combined effect. We used a level of significance of 5%.

Gestational length was used to identify conception date. There were only 330 (0.6%) pregnancies with missing values for gestational length but the proportion of still births among these was statistically significant higher (15.4%) than among other pregnancies (0.4%). We therefore substituted the missing values by the mean value of gestational length for live (278 days) and still

(220 days) births, respectively.

We performed the following sensitivity analyses: (i) restricted to nulliparous women (N=9 660), (ii) with pre-eclampsia as the outcome (N=18 724), and (iii) restricted to the first trimester as the exposure time (N=18 158). In the latter analysis, night workers had at ≥1 night shift and day workers ≥1 day shift but no night, evening or early morning shifts during the first 12 pregnancy weeks instead of 20 weeks applied in the main analysis.

All analyses were done with the SAS 9.4 software (SAS Institute, Cary, North Carolina, United States).

Results

In our cohort of 18 724 pregnant women, 11 193 were classified as night workers and 7531 as day workers (table 1). The most frequent occupations were nurse (44%), physician (13%), medical secretary (7%), physio/occupational therapist (5%) and laboratory technician (4%) reflecting that the majority of the workers covered by the DWHD are employed at hospitals. Characteristics of day

Table 1. Characteristics of pregnant workers in public administration and hospitals in Denmark, 2007–2013. [SD=standard deviation.]

	Day work [a] (N=7531)				Night work [b] (N=11 193)			
	N	%	Mean	SD	N	%	Mean	SD
Age (years)			31.8	4.2			30.7	3.9
Body mass index (kg/m²)			24.0	7.6			23.9	7.9
Parity								
1	3462	46.0			6198	55.4		
2	2596	34.5			3156	28.2		
≥3	1356	18.0			1701	15.2		
Smoking								
Non smoker	6952	92.3			10 319	92.2		
Former smoker	106	1.4			230	2.1		
Smoker	273	3.6			309	2.8		
Socioeconomic status								
High	1844	24.5			2618	23.4		
Medium	3848	51.1			7575	67.7		
Low	1821	24.2			988	8.8		
Most frequent [c] occupations								
Nurse	1071	14.2			6,857	61.3		
Physician	659	8.8			2,000	17.9		
Nurse assistant	208	2.8			390	3.5		
Laboratory technician	503	6.7			259	2.3		
Midwife	10	0.1			248	2.2		
Medical secretary	1314	17.5			58	0.5		
Physio- and ergo therapist	977	13.0			30	0.3		
Cleaning and kitchen staff	391	5.2			8	0.07		
Psychologist	463	6.2			1	0.01		
Shifts during the first 20 weeks of pregnancy								
Day			65.9	23.8			37.9	17.2
Night							11.2	9.1
Evening							9.2	9.7
Early morning							0.03	0.8
Weekly working hours [d]			23.8	8.9			25.1	7.7
Sickness absence days 3 months prior to pregnancy			2.9	7.2			2.6	5.6

[a] ≥1 day shift and no night, evening or early morning shift during the first 20 pregnancy weeks.
[b] ≥1 night shift during the first 20 pregnancy weeks.
[c] Occupations with ≥100 subjects.
[d] Paid and unpaid leave excluded.

and night workers were rather similar. Day workers had a total of 496 024 day shifts during the first 20 weeks of pregnancy. Night workers had a total of 652 858 shifts being 65% day shifts and 19% night shifts. Only 113 women (1%) worked fixed night shifts. They had higher BMI (mean 25.2 kg/m², SD 5.0), higher proportion of women with parity ≥3 (27%), higher proportion of current smokers (4.4%) and higher proportion of women with low SES (43%) compared to the other night workers in the cohort. The prevalence of HDP was 3.6% among day workers and 3.8% among night workers.

Women working ≥1 spell of ≥4 consecutive night shifts during the first 20 pregnancy weeks had higher risk of HDP compared to night workers without consecutive night shifts (OR 1.41, 95% CI 1.01–1.98), see table 2. We furthermore observed a statistically significant trend of increasing risk with increasing number of consecutive night shifts. Women with spells of exclu-

Table 2. Odds ratios (OR) of hypertensive disorders of pregnancy by consecutive night shifts during the first 20 pregnancy weeks among workers in public administration and hospitals in Denmark, 2007–2013. [CI=confidence interval]

Consecutive night shifts	Women		Cases		Model 1 [a]		Model 2 [b]	
	N	%	N	%	OR	95% CI	OR	95% CI
All workers (N=18 724)								
Day work [c]	7531	40.2	270	3.6	1.00	Referent	1.00	Referent
0	4003	21.4	132	3.3	0.92	0.74–1.13	0.85	0.67–1.08
2–3	5225	27.9	205	3.9	1.10	0.91–1.32	0.97	0.79–1.20
≥4	1965	10.5	89	4.5	1.28	0.99–1.62	1.13	0.86–1.48
P for trend						0.05		0.62
Night workers [d] (N=11 193)								
0	4003	35.8	132	3.3	1.00	Referent	1.00	Referent
2–3	5225	46.7	205	3.9	1.20	0.96–1.50	1.22	0.92–1.62
≥4	1965	17.6	89	4.5	1.39	1.06–1.83	1.41	1.01–1.98
P for trend						0.02		0.04

[a] Crude analysis.
[b] Adjusted for categories of age, body mass index, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.
[c] ≥1 day shift and no night, evening or early morning shift during the first 20 pregnancy weeks.
[d] ≥1 night shift during the first 20 pregnancy weeks.

Table 3. Odds ratios (OR) of hypertensive disorders of pregnancy by number of quick returns [a] and quick returns after a night shift [b] during the first 20 pregnancy weeks among workers in public administration and hospitals in Denmark, 2007–2013. [CI=confidence interval]

	Women		Cases		Model 1 [c]		Model 2 [d]	
	N	%	N	%	OR	95% CI	OR	95% CI
Quick returns								
All workers (N=18 724)								
Day work [e]	7531	40.2	270	3.6	1.00	Referent	1.00	Referent
0	3817	20.4	128	3.4	0.93	0.75–1.15	0.92	0.72–1.16
1–4	5123	27.4	203	4.0	1.11	0.92–1.34	1.00	0.81–1.23
≥5	2253	12.0	95	4.2	1.18	0.93–1.50	0.94	0.72–1.22
P for trend						0.10		0.76
Night workers [f] (N=11 193)								
0	3817	34.1	128	3.4	1.00	Referent	1.00	Referent
1–4	5123	45.8	203	4.0	1.19	0.95–1.49	1.12	0.87–1.45
≥5	2253	20.1	95	4.2	1.27	0.97–1.66	1.07	0.79–1.46
P for trend						0.07		0.64
Quick returns after a night shift								
All workers (N=18 724)								
Day work [e]	7531	40.2	270	3.6	1.00	Referent	1.00	Referent
0	1023	5.5	39	3.8	1.07	0.75–1.48	0.84	0.55–1.23
1–4	4569	24.4	160	3.5	0.98	0.80–1.19	0.86	0.69–1.07
≥5	5601	29.9	227	4.1	1.14	0.95–1.36	1.06	0.87–1.29
P for trend						0.26		0.74
Night workers [f] (N=11 193)								
0	1023	9.1	39	3.8	1.00	Referent	1.00	Referent
1–4	4569	40.8	160	3.5	0.92	0.65–1.33	1.03	0.69–1.59
≥5	5601	50.0	227	4.1	1.07	0.76–1.53	1.28	0.87–1.95
P for trend						0.30		0.05

[a] <11 hours between two consecutive shifts.
[b] <28 hours between a night shift and the consecutive shift.
[c] Crude analysis.
[d] Adjusted for categories of age, body mass index, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.
[e] ≥1 day shift and no night, evening or early morning shift during the first 20 pregnancy weeks.
[f] ≥1 night shift during the first 20 pregnancy weeks.

Table 4. Odds ratios (OR) of hypertensive disorders of pregnancy by duration of night shifts during the first 20 pregnancy weeks among workers in public administration and hospitals in Denmark, 2007–2013. [CI=confidence interval]

Duration of night shifts	Women		Cases		Model 1 [a]		Model 2 [b]	
	N	%	N	%	OR	95% CI	OR	95% CI
All workers (N=18 724)								
Day work [c]	7531	40.2	270	3.6	1.00	Referent	1.00	Referent
<12 hours [d]	5734	30.6	214	3.7	1.04	0.87–1.25	0.94	0.76–1.16
≥12 hours [e]	5459	29.2	212	3.9	1.09	0.90–1.31	1.00	0.81–1.23
P for trend					0.37		0.92	
Night workers [f] (N=11 193)								
<12 hours	5734	51.2	214	3.7	1.00	Referent	1.00	Referent
≥12 hours	5459	48.8	212	3.9	1.04	0.86–1.27	1.08	0.85–1.36

[a] Crude analysis.
[b] Adjusted for categories of age, body mass index, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.
[c] ≥1 day shift and no night, evening or early morning shift during the first 20 pregnancy weeks.
[d] ≥1 night of <12 hours and no night shifts of ≥12 hours.
[e] ≥1 night shift of ≥12 hours.
[f] ≥1 night shift during the first 20 pregnancy weeks.

Table 5. Odds ratios (OR) of hypertensive disorders of pregnancy by number of night shifts during the first 20 pregnancy weeks among workers in public administration and hospitals in Denmark, 2007–2013. [CI=confidence interval]

Number of night shifts	Women		Cases		Model 1 [a]		Model 2 [b]	
	N	%	N	%	OR	95% CI	OR	95% CI
All workers, N=18 724								
Day work [c]	7531	40.2	270	3.6	1.00	Referent	1.00	Referent
1–19	9560	51.1	360	3.8	1.05	0.90–1.24	0.94	0.78–1.12
≥20	1633	8.7	66	4.0	1.13	0.85–1.48	1.09	0.81–1.45
P for trend					0.35		0.96	
Night workers [d], N=11 193								
1–19	9560	85.4	360	3.8	1.00	Referent	1.00	Referent
≥20	1633	14.6	66	4.0	1.08	0.82–1.40	1.15	0.86–1.52

[a] Crude analysis.
[b] Adjusted for categories of age, body mass index, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.
[c] ≥1 day shift and no night, evening or early morning shift during the first 20 pregnancy weeks.
[d] ≥1 night shift during the first 20 pregnancy weeks.

sively 2–3 consecutive night shifts had, on average, 4 consecutive night shifts in total. While women with ≥1 spell of ≥4 consecutive night shifts had, on average, 14 consecutive night shifts in total. Hence these categories express both length of spells and total number of consecutive night shifts.

As shown in table 3, we observed a statistically significant trend of increasing risk of HDP with increasing number of quick returns after night shifts. However, the risk estimate for the highest exposed group, those with ≥5 quick returns after a night shift (on average 10.4 quick returns) during the first 20 pregnancy weeks, did not reach statistical significance (OR 1.28, 95% CI 0.87–1.95).

Table 4 presents the results for long-night-shift workers compared to day workers (OR 1.00, 95% CI 0.81–1.23), and compared to short-night-shift workers (OR 1.08, 95% CI 0.85–1.36). Of all long night shifts, 40% lasted 17–24 hours and 34% lasted 9–16 hours, while 62% of all short night shifts lasted ≤8 hours.

Table 5 presents the results for women who worked ≥20 night shifts during the first 20 pregnancy weeks (on average 28 night shifts) compared to day workers (OR 1.13, 95% CI 0.85–1.48), and compared to women working 1–19 night shifts (OR 1.15, 95% CI 0.86–1.52).

Further adjustment for number of night shifts (model 3) did not substantially change the results in the analyses of consecutive night shifts, quick returns and duration of night shifts.

The association between night work and HDP was modified by BMI (P-value for multiplicative interaction 0.03). As presented in table 6, analysis among women with BMI ≥30 kg/m^2 revealed that those who worked ≥4 consecutive night shifts had substantially increased risk of HPD compared to day workers (OR 5.31, 95% CI 1.98–14.22). The corresponding risk for women with BMI <25 kg/m^2 was OR 1.02, 95% CI 0.73–1.41. Further adjustment for BMI among obese women did not change the results. A similar increase was observed for all exposures among obese women (see supplementary tables S1-S4, www.sjweh.fi/show_abstract. php?abstract_id=3728). Due to low statistical power we were unable to make stratified comparisons within night workers only. We found no interaction of any of the analyzed exposures with maternal age or SES.

Overall sensitivity analyses slightly attenuated the estimates across all exposures. The effect of consecutive night shifts during the first 20 pregnancy weeks was con-

Table 6. Odds ratios (OR) of hypertensive disorders of pregnancy by consecutive night shifts during the first 20 pregnancy weeks stratified [a] by body mass index (BMI) among workers in public administration and hospitals in Denmark, 2007–2013. [CI=confidence interval]

Consecutive night shifts	Women		Cases		Model1 [b]		Model2 [c]	
	N	%	N	%	OR	95% CI	OR	95% CI
BMI <25 kg/m^2 (N=12 815)								
Day work	5119	40.0	201	3.9	1.00	Referent	1.00	Referent
0	2952	23.0	96	3.3	0.82	0.64–1.05	0.77	0.59–1.02
2–3	3545	27.7	154	4.3	1.11	0.90–1.38	0.95	0.75–1.21
≥4	1199	9.4	56	4.7	1.20	0.89–1.62	1.02	0.73–1.41
BMI 25–29 kg/m^2 (N=3501)								
Day work	1419	40.5	52	3.7	1.00	Referent	1.00	Referent
0	644	18.4	24	3.7	1.02	0.62–1.67	0.93	0.55–1.56
2–3	994	28.4	40	4.0	1.10	0.72–1.68	0.97	0.63–1.51
≥4	444	12.7	16	3.6	0.98	0.56–1.74	0.94	0.53–1.69
BMI ≥ 30 kg/m^2 (N=1588)								
Day work	671	42.3	7	1.0	1.00	Referent	1.00	Referent
0	229	14.4	10	4.4	4.33	1.63–11.52	3.47	1.15–10.52
2–3	435	27.4	8	1.8	1.78	0.64–4.94	1.60	0.53–4.83
≥4	253	15.9	13	5.1	5.14	2.03–13.03	5.31	1.98–14.22

[a] P–value for multiplicative interaction 0.0317.
[b] Crude analysis.
[c] Adjusted for categories of age, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.

sistent although not statistically significant throughout sensitivity analyses within night workers (OR 1.39, 95% CI 0.94–2.05 restricted to nulliparous women, OR 1.40, 95% CI 0.91–2.15 with pre-eclampsia as the outcome, and OR 1.36, 95% CI 0.96–1.93 with the first trimester as the exposure time). Regarding the question on possible selection out of night work during pregnancy, we identified only 580 women (5%) who worked at least one night shift during the first trimester and changed to fixed day work during the second trimester. These women had similar age (mean 31 years), BMI (mean 23.7 kg/m^2) and smoking habits (2.8% current smokers) as the rest of the cohort but presented a higher proportion of physicians (37%).

Discussion

To our knowledge, this is the first study to investigate the association between HDP with different dimensions of night work objectively assessed through payroll data. In our study, workers with ≥4 consecutive night shifts during the first 20 pregnancy weeks had higher risk of HDP compared to night workers without consecutive night shifts (OR 1.41, 95% CI 1.01–1.98). We furthermore observed a dose−response gradient for number of consecutive night shifts and the risk of HDP. The fact that this effect was observed in comparisons within night workers strengthens the evidence of a causal effect as the group of night workers is more homogeneous. These analyses may therefore be less susceptible to the healthy worker effect present in comparisons of night versus day workers. In fact, we observed higher risk estimates in comparisons within night workers for all the expo-

sures. Comparisons within night workers may be more appropriate from an epidemiological point of view. On the other hand, analyses restricted to night workers exclude an unexposed group and some selection bias regarding different dimensions of night work remains. Previous studies have shown that individual preferences related to both personal (chronotype, sleep flexibility, social context) (51–53) and occupational (work content, demands and environment) (54) factors vary substantially among night workers resulting in differences in adaptation to night work. Accordingly we found that workers with fixed night work during the first 20 pregnancy weeks differed in BMI, parity, smoking habits and SES compared to the other night workers in the cohort. Compared to the background Danish population, our cohort presented lower prevalence of smoking during pregnancy (3% versus 12%) (55) and lower proportion of overweight women (19% versus 46%) (56), which may reflect a more health promoting behavior among healthcare professionals.

Our findings are in accordance with recent studies focusing on consecutive night shifts rather than solely on the number of night shifts. For example increasing the number of consecutive night shifts has been associated with progressive changes in hormones involved in circadian regulation, such as melatonin, cortisol, thyroxin and prolactin (30, 31, 57). Such changes have been observed down to three consecutive night shifts (58, 59). Furthermore, it has been suggested that at least two days off work are required to allow for circadian readjustment following 2–4 consecutive night shifts (31, 60). In our cohort, the majority of hospital employees had rotating shifts with different schedules nearly every week which do not fulfill this recommendation. Hence, in this context, working consecutive night shifts may

lead both to circadian disruption and to insufficient recovery. Our findings of increasing odds ratios of HDP with increasing number of quick returns after night shifts also support the potential effect of insufficient recovery after a night shift.

In our data, BMI modified the effect of night work on the risk of HDP, as obese women who worked longer night shifts, longer spells of consecutive night shifts and had the highest number of quick returns after night shifts had 4–5 fold increased risk of HDP compared to day workers. It is known that pre-pregnancy BMI is an important risk factor for HDP independent of weight gain during pregnancy (17, 61, 62). Even though these results are based on few cases, they are consistent across exposures. Obese women neither had higher proportion of workers with fixed night shifts nor a gradient of increasing BMI from day to night workers.

We hypothesized that women who worked night shifts during the first trimester and changed working schedule to only day work during the second trimester due to health problems might cause bias towards the null as the exposure time in the main analysis was 20 weeks. However, sensitivity analysis resetting exposure time to the first 12 pregnancy weeks indicated no such bias. On the other hand, analysis restricted to the first trimester excludes a possible effect of night work during the second trimester, which may in part explain the attenuation of the estimates. Even though the physiopathology of HDP seems to be related with placenta development in the beginning of pregnancy (14), demographic and lifestyle factors on the second and third trimester of pregnancy seem also to influence the risk of HDP (63).

We found no statistically significant association between HDP with any of the analyzed dimensions of night work compared to day workers, suggesting that the effect of night work on the risk of HDP is related to the way night shifts are organized rather than the mere presence of night shifts. This can be in part due to differences in work content and work environment between day and night workers. We did not observe the presence of more pronounced risk factors for HDP among night workers compared to day workers. Actually our cohort of night workers had lower BMI, a lower proportion of smokers and a lower proportion of workers with low SES than day workers. Similar to our results, three out of four previous studies that compared shift workers with day workers found no association between with HDP (37, 39, 40). Wergeland & Strand (38) reported an increased prevalence of pre-eclampsia among shift workers, but only among parous women.

The main strengths of our study are the large and national sample size, the objective and detailed exposure assessment, and the use of validated and objective registries for identification of covariates and outcomes, which makes information bias and selection in and out

of the study unlikely. Furthermore, we evaluated different dimensions of night work within night workers and restricted the exposure time to specific periods of pregnancy. Some limitations include a lack of information on workload during night shifts, such as the possibility for sleep during on call shifts, and on chronotype and personal preferences of the participants. The latter is especially relevant because night work is compulsory for the majority of occupations in our cohort. Additionally, our study design did not account for the healthy worker effect, where women with health problems in general tend to choose day work. As our cohort comprises primarily healthcare professionals, our results may not apply for pregnant workers in other occupations.

Ideally future studies on health effects of night work during pregnancy should combine objectively assessed work schedules with information on chronotype and personal preferences, work content and environment, and should perform comparisons both with day workers and within groups of night workers.

Concluding remarks

In this nationwide study of Danish pregnant workers in the public health sector with objectively assessed work schedules, working consecutive night shifts and quick returns after night shifts during the first 20 pregnancy weeks was associated with an increased risk of HDP, in particular among obese women. Possible ways for avoiding such risk when organizing night work during pregnancy are favoring single night shifts or short spells of consecutive night shifts and reducing quick returns by allowing for adequate recovery time following night shifts.

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Night work and hypertensive disorders of pregnancy: a national register-based cohort study [1]

by Paula Hammer, MD,[2] Esben Flachs, MSc, PhD, Ina Specht, MSc, PhD, Anja Pinborg, MD, PhD, Sesilje Petersen, MSc, PhD, Ann Larsen, MSc, PhD, Karin Hougaard, MSc, PhD, Johnni Hansen, MSc, PhD, Åse Hansen, MSc, PhD, Henrik Kolstad, PhD, Anne Garde, PhD, Jens Peter Bonde, MD, PhD

1   Supplementary material

2   Correspondence to: Paula EC Hammer, Bispebjerg Bakke 23, indgang 20F, 2400 Copenhagen, Denmark. [E-mail: paulahammer@dadlnet.dk]

Table S1. Odds ratios of hypertensive disorders of pregnancy by number of night shifts during the first 20 pregnancy weeks stratified [a] by body mass index (BMI) among workers in public administration and hospitals in Denmark, 2007–2013. [OR = odds ratio; CI = confidence interval]

Number of night shifts	Women		Cases		Model1 [b]		Model2 [c]	
	N	%	N	%	OR	95% CI	OR	95% CI
BMI < 25 kg/m², N=12,815								
Day work	5119	40.0	201	3.9	1.00	Referent	1.00	Referent
1-19	6698	52.2	266	4.0	1.01	0.84-1.22	0.89	0.73-1.09
≥ 20	998	7.8	40	4.0	1.02	0.72-1.44	0.93	0.65-1.34
BMI 25-29 kg/m², N=3,501								
Day work	1419	40.5	52	3.7	1.00	Referent	1.00	Referent
1-19	1719	49.1	63	3.7	1.00	0.69-1.45	0.89	0.60-1.32
≥ 20	363	10.4	17	4.7	1.29	0.74-2.26	1.25	0.70-2.21
BMI ≥ 30 kg/m², N=1,588								
Day work	671	42.2	7	1.0	1.00	Referent	1.00	Referent
1-19	713	44.9	24	3.4	3.30	1.41-7.72	2.87	1.14-7.22
≥ 20	204	12.9	7	3.4	3.37	1.17-9.72	3.71	1.22-11.23

[a] P-value for multiplicative interaction 0.1065.

[b] Crude analysis.

[c] Adjusted for categories of age, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.

Table S2. Odds ratios of hypertensive disorders of pregnancy by duration of night shifts during the first 20 pregnancy weeks stratified [a] by body mass index (BMI) among workers in public administration and hospitals in Denmark, 2007–2013. [OR = odds ratio; CI = confidence interval]

Duration of night shifts	Women		Cases		Model1 [b]		Model2 [c]	
	N	%	N	%	OR	95% CI	OR	95% CI
BMI < 25 kg/m², N=12,815								
Day work	5119	40.0	201	3.9	1.00	Referent	1.00	Referent
< 12 hours	3749	29.2	150	4.0	1.02	0.82-1.26	0.89	0.70-1.12
≥ 12 hours	3947	30.8	156	4.0	1.01	0.81-1.25	0.91	0.72-1.15
BMI 25-29 kg/m², N=3,501								
Day work	1419	40.5	52	3.7	1.00	Referent	1.00	Referent
< 12 hours	1141	32.6	43	3.8	1.03	0.68-1.55	0.91	0.59-1.40
≥ 12 hours	941	26.9	37	3.9	1.08	0.70-1.65	1.00	0.64-1.57
BMI ≥ 30 kg/m², N=1,588								
Day work	671	42.3	7	1.0	1.00	Referent	1.00	Referent
< 12 hours	580	36.5	14	2.4	2.35	0.94-5.85	2.25	0.85-5.99
≥ 12 hours	337	21.2	17	5.0	5.04	2.07-12.27	4.55	1.72-12.04

[a] P-value for multiplicative interaction 0. 0369.

[b] Crude analysis.

[c] Adjusted for categories of age, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.

Table S3. Odds ratios of hypertensive disorders of pregnancy by number of quick returns [a] during the first 20 pregnancy weeks stratified [b] by body mass index (BMI) among workers in public administration and hospitals in Denmark, 2007–2013. [OR = odds ratio; CI = confidence interval]

Quick returns	Women		Cases		Model1 [c]		Model2 [d]	
	N	%	N	%	OR	95% CI	OR	95% CI
BMI < 25 kg/m², N=12,815								
Day work	5119	40.0	201	3.9	1.00	Referent	1.00	Referent
0	2661	20.8	86	3.2	0.82	0.63-1.06	0.79	0.59-1.04
1-4	3468	27.0	150	4.3	1.11	0.89-1.37	0.97	0.77-1.23
≥ 5	1567	12.2	70	4.5	1.14	0.86-1.51	0.89	0.66-1.20
BMI 25-29 kg/m², N=3,501								
Day work	1419	40.5	52	3.7	1.00	Referent	1.00	Referent
0	691	19.7	29	4.2	1.15	0.72-1.83	1.09	0.67-1.78
1-4	980	28.0	34	3.5	0.94	0.61-1.47	0.86	0.54-1.35
≥ 5	411	11.7	17	4.1	1.13	0.65-1.98	0.96	0.54-1.71
BMI ≥ 30 kg/m², N=1,588								
Day work	671	42.3	7	1.0	1.00	Referent	1.00	Referent
0	308	19.4	11	3.6	3.51	1.35-9.15	3.51	1.26-9.80
1-4	440	27.7	14	3.2	3.12	1.25-7.79	3.06	1.15-8.16
≥ 5	169	10.6	6	3.6	3.49	1.16-10.53	2.29	0.64-8.26

[a] Less than 11 hours between two consecutive shifts.

[b] P-value for multiplicative 0. 1309.

[c] Crude analysis.

[d] Adjusted for categories of age, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.

Table S4. Odds ratios of hypertensive disorders of pregnancy by number of quick returns after a night shift [a] during the first 20 pregnancy weeks stratified [b] by body mass index (BMI) among workers in public administration and hospitals in Denmark, 2007–2013. [OR = odds ratio; CI = confidence interval]

Quick returns after a night shift	Women		Cases		Model1 [c]		Model2 [d]	
	N	%	N	%	OR	95% CI	OR	95% CI
BMI < 25 kg/m², N=12,815								
Day work	5119	40.0	201	3.9	1.00	Referent	1.00	Referent
0	704	5.5	30	4.3	1.09	0.74-1.61	0.86	0.55-1.35
1-4	3204	25.0	116	3.6	0.92	0.73-1.16	0.79	0.61-1.02
≥ 5	3788	29.5	160	4.2	1.08	0.87-1.33	0.99	0.79-1.25
BMI 25-29 kg/m², N=3,501								
Day work	1419	40.5	52	3.7	1.00	Referent	1.00	Referent
0	192	5.5	5	2.6	0.70	0.28-1.78	0.55	0.19-1.55
1-4	816	23.3	37	4.5	1.25	0.81-1.92	1.10	0.70-1.74
≥ 5	1074	30.7	38	3.5	0.96	0.63-1.48	0.91	0.58-1.41
BMI ≥ 30 kg/m², N=1,588								
Day work	671	42.3	7	1.0	1.00	Referent	1.00	Referent
0	82	5.2	3	3.7	3.60	0.91-14.21	2.84	0.56-14.42
1-4	336	21.1	5	1.5	1.43	0.45-4.55	1.13	0.32-4.06
≥ 5	499	31.4	23	4.6	4.58	1.95-10.77	4.55	1.81-11.42

[a] Less than 28 hours between a night shift and the consecutive shift.

[b] P-value for multiplicative 0. 0117.

[c] Crude analysis.

[d] Adjusted for categories of age, smoking, socioeconomic status, parity and sickness absence three months prior to pregnancy.

Paper II (in press, Journal of Occupational and Environmental Medicine, December 2018)

Night work and sick leave during pregnancy: a national register-based within-worker cohort study

Hammer PEC, Garde AH, Begtrup LM, Flachs EM, Hansen J, Hansen ÅM, Hougaard KS, Kolstad HA, Larsen AD, Pinborg AB, Specht IO, Bonde JP.

NIGHT WORK AND SICK LEAVE DURING PREGNANCY:

A NATIONAL REGISTER-BASED WITHIN-WORKER COHORT STUDY

Paula E C Hammer[1], Anne H Garde[2,3], Luise M Begtrup[1], Esben M Flachs[1], Johnni Hansen[4], Åse M Hansen[2,3], Karin S Hougaard[2], Henrik A Kolstad[5], Ann D Larsen[2], Anja Pinborg[6], Ina O Specht[7], Jens Peter Bonde[1,3]

[1] Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark.

[2] National Research Centre for the Working Environment, Copenhagen, Denmark.

[3] University of Copenhagen, Department of Public Health, Copenhagen, Denmark.

[4] Danish Cancer Society Research Centre, Copenhagen, Denmark.

[5] Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark.

[6] Fertility Clinic, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark.

[7] The Parker Institute, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark.

Corresponding author
Paula Edeusa Cristina Hammer
Bispebjerg Bakke 23, indgang 20F - 2400 Copenhagen, Denmark
e-mail: paulahammer@dadlnet.dk
Telephone: +45 38 63 61 72 Mobile: +45 51 23 74 35 Fax: +45 38 63 98 34

ABSTRACT

Objective

The aim of our study was to investigate the acute effect of night work during pregnancy on the risk of calling in sick the following day using register-based information and the workers as their own controls.

Methods

Using the payroll based national Danish Working Hour Database, including all public hospital employees in Denmark, we identified 9 799 pregnant women with ≥ 1 day shift and ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks from January 2007 to December 2013. We performed fixed effects logistic regression, i.e. within-worker comparisons, of the risk of sick leave of any duration starting within 24 hours after night shifts of different length versus day shifts.

Results

Most of the participants were nurses (64%) or physicians (16%). We found an increased relative risk of sick leave following night shifts compared to day shifts during all pregnancy trimesters. The risk was highest for night shifts lasting > 12 hours (OR 1.37, 95% CI 1.15-1.63 for nurses; OR 1.87, 95% CI 1.69-2.08 for physicians), and among women aged > 35 years (OR 1.42, 95% CI 1.24-1.63).

Conclusion

Among Danish public hospital employees night shifts during pregnancy, especially shifts longer than 12 hours, increased the risk of calling in sick the following day independent of personal factors and time-invariant confounders in all pregnancy trimesters.

KEY MESSAGES

1. **What is already known about this topic?**

   Shift work during pregnancy may be associated with increased risk of sick leave. However, prior studies presented crude assessment of working schedules, lack of pregnancy period-specific analysis, information bias and healthy worker selection.

2. **What are the new findings?**

   Among Danish public hospital employees night shifts during pregnancy, especially shifts longer than 12 hours, increased the risk of calling in sick the following day independent of personal factors and time-invariant confounders in all pregnancy trimesters.

3. **How might this impact on policy or clinical practice in the foreseeable future?**

   If pregnant women work at night, reducing the frequency and duration of night shifts in the organization of their working schedules may reduce sick leave during pregnancy.

INTRODUCTION

A high prevalence of long-term (> 14 consecutive days) sick leave among European pregnant workers has been demonstrated (1-3). The primary reason for that seems to be pregnancy-related but a mismatch between pregnancy and work, for instance work-family conflicts, workload and reproductive occupational hazards, (4-7), and different polices for sick leave during pregnancy across countries also play a role (3). Women not covered by paid sick leave during pregnancy might have higher threshold for calling in sick due to economic challenges. Recently published studies found that nearly 10% of the women with long-term sick leave during pregnancy reported work-related reasons for sick leave (1, 3).

Shift work during pregnancy has in Danish studies been associated with an increased risk of long-term sick leave, including a dose-effect relationship with increasing number of night shifts (1, 5, 8, 9). To our knowledge, there are no studies on short-term (≤ 14 consecutive days) sick leave during pregnancy. It is possible that short- and long-term sick leave during pregnancy in relation to night work might involve different factors, but this is yet to be elucidated.

One of the mechanisms connecting night work with sick leave involves fatigue and disturbed sleep, both sleep length and quality, leading to lack of recovery (10-13). Härmä and colleagues found, in a recently published study, that night shifts were associated with fatigue, both during work and free days, altered sleep length and difficulties to fall asleep (14). In a 2-years prospective cohort of truck drivers need for recovery after work predicted sick leave of > 14 days (15). The acute effect of night shifts, including night shifts lasting up to 12 hours, on sleep and fatigue among healthcare workers has been shown in epidemiological and field studies (16-19). There is however a lack of studies on health effects of night shifts longer than 12 hours.

Crude assessment of working schedules, lack of pregnancy period-specific analysis, information bias, and healthy worker selection challenge the results from prior studies. Furthermore, sick leave is closely related to personal factors, which is an important source of bias in comparisons between individuals.

We aimed to investigate the acute effect of night shifts of different length during pregnancy on the risk of calling in sick within 24 hours after a shift regardless the duration of sick leave. We hypothesized that night shifts lead to lack of recovery and hereby increased the risk of sick leave in the subsequent day. The novel aspects of our study are the register-based assessment of exposure and outcome, and within-worker comparisons in a prospective design.

METHODS

Design

We conducted a prospective nationwide register-based cohort study using the participants as their own controls. We used information from two Danish national registries linked on the individual level via the civil registration number given to all residents in Denmark since 1968.

The Danish Working Hour Database (DWHD), a national payroll database covering more than 250 000 employees in the Danish administrative regions including all public hospital employees, provided the source population. It includes daily information on time of start and end of shifts and all types of paid and unpaid leave, job title and place of employment from January 2007 to December 2015 (20). Information on pregnancy and covariates were identified from The Danish Medical Birth Registry, which contains information on all births in Denmark since 1973 (21).

Study cohort

The study cohort was retrieved from the same source population as in a recently published study (22). In short, it comprised 42 485 women from the DWHD who gave birth at least once during from January 2007 to December 2013, giving a total of 60 482 pregnancies. We excluded women ≤ 18 and ≥ 50 years (N=15), multiple pregnancies (N=2 957) and pregnancies conceived in 2006 (N=6 403), because they lacked payroll data, and thereby exposure data, from conception to January 2007. Further, we excluded pregnancies if employment in one the administrative Regions of Denmark, and therefore registration in the DWHD, started after conception or ended before 32 pregnancy weeks (N=16 570) to ensure that payroll data was available throughout the first 32 pregnancy weeks. We conducted fixed effects analysis, which requires change in both the exposure and the outcome for each participant (23). Therefore, the study population comprised women with both ≥ 1 day shift, ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks (N=23 024 excluded). Finally, each woman contributed with only their first pregnancy occurring during the study period (N=1 714 pregnancies excluded), leaving 9 799 women eligible for analyses (supplemental figure).

Supplemental figure. Flowchart of the identification of the study population.

Danish Working Hour Database:
265 702 public hospital employees

Linkage with Medical Birth Registry

60 482 pregnancies from 42 485 women who have given birth at least once between January 2007 and December 2013

Excluded

Age < 18 or > 50 years old (N=15 pregnancies)

Multiple pregnancies (N=2957)

Conception in 2006 (N=6403 pregnancies)

(N=16 570 pregnancies)

None day shift, night shift or sick leave (N= 23 024 pregnancies)

Recurrent pregnancies (N=1714)

9 799 women eligible for analyses

Exposure

Risk days were days with a DWHD registration other than maternity leave, vacation, unpaid leave and compulsory day off preceded by a day or a night shift within a 24-hour period.

Shifts during the first 32 pregnancy weeks, including on-call shifts, lasting ≥ 3 hours were defined as day (start time after 06:00 and end time before 21:00) or night (any start and end time including any duration of working hours between 23:00 and 06:00) corresponding to 84 % of all registered shifts, the rest being evening or early morning shifts. The duration of night shifts was defined as ≤ 8 hours, > 8-12 hours or > 12 hours (long night shifts).

Outcome

The outcome was defined as a DWHD registration of sick leave lasting ≥ 3 hours. Registrations with consecutive dates of sick leave were collapsed with the date of the first and last registration defining the duration of the sick leave period.

Registrations coded as 'exacerbated pregnancy symptoms' or 'pregnancy complications' (pregnancy leave) were used for descriptive purposes to assess the total absence during pregnancy. They reflected pregnancy leave mostly due to medical complications and not ordinary sick leave. Administrative procedures for registration of pregnancy leave differ from registrations of sick leave, and they vary across the five administrative Regions of Denmark. Registrations of pregnancy leave were therefore not appropriate to investigate the risk of calling in sick within 24 hours after a shift. The combined effect of both sick leave and pregnancy leave was investigated in sensitivity analysis.

Demographic characteristics

Age (<30, 30-35, >35 years), body mass index (BMI, <25, 25-29, ≥ 30 kg/m^2), parity (1, 2, ≥ 3), and smoking (nonsmoker, former smoker, smoker) registered by the midwife or family doctor at the first antenatal visit were retrieved from The Danish Medical Birth Registry.

Classification of socioeconomic status (SES) into high, low or medium was derived from Statistics Denmark and was based on DISCO-88, the Danish version of the International Standard Classification of Occupations from 2007-2009 and 2010-2013 (ISCO-88 and DISCO-08), respectively (24, 25).

We considered age, BMI and occupation as potential effect modifiers. The reason for the latter is that different occupations have different organization of working schedules and work content, i.e. different tasks and workload.

Statistical analyses

We compared the risk of sick leave of any duration starting within 24 hours after night shifts of different length versus day shifts during the first 32 pregnancy weeks using the participants as their own controls. We performed fixed effects logistic regression to account for repeated measures within workers. This statistical method requires that each participant has change in both the exposure and the outcome, as it in praxis, answers the question: "Does a change in the exposure cause a change in the outcome?" (23).Results were presented as odds ratios (OR) with 95% confidence intervals (CI).

For interaction analysis with age, BMI and occupation we used a likelihood ratio test comparing models with and without the interaction term. As nurses and physicians represented most of the cohort, we limited stratified analyses to these occupations. We performed sensitivity analyses restricted to nulliparous women and using both sick leave and pregnancy leave as the outcome.

We used two-tailed tests with a significance level of 0.05. All analyses were done with the SAS 9.4 software (SAS Institute, Cary, North Carolina, United States).

RESULTS

The study cohort comprised 9 799 women contributing to 474 338 risk days. Around 65% were nurses and 16% physicians. Table 1 presents the participant's personal and working time characteristics. Of all shifts included in the analyses 82 % were day and 18% night shifts. Nurses and physicians had similar number of night shifts, while physicians had more day shifts than nurses (table 1). Around 42% of the night shifts lasted ≤ 8 hours, 35% lasted > 8-12 hours and 23% lasted > 12 hours. The proportion of long night shifts was 7% among nurses and 99% among physicians (table 1). These differences reflect different collective agreements for nurses and physicians in Denmark (26, 27). Nurses had more than twice as many days of absence during the first 32 pregnancy weeks (mean 34.4, median 17.0, SD 38.9) than physicians (mean 15.7, median 6.0, SD 25.9) – table 1.

Table 1. Characteristics of 9799 pregnant public hospital employees [a] in Denmark, 2007–2013.

	N	%	Mean	Standard deviation
Age, years			30.9	3.9
Body Mass Index, kg/m^2			23.8	4.5
Parity				
1	5095	52.0		
2	3061	31.2		
≥ 3	1527	15.6		
Smoking				
Non- smoker	9067	92.6		
Former smoker	191	2.0		
Smoker	265	2.7		
Socioeconomic Status				
Low	670	6.9		
Medium	6973	71.4		
High	2118	21.7		
Most Frequent Occupations				
Nurse	6334	64.6		
Physician	1593	16.3		
Nurse assistant	572	5.8		
Laboratory technician	259	2.6		
Midwife	207	2.1		
Care worker	138	1.4		
Number of day shifts [b]				
All women			60.7	25.4
Nurses			57.5	22.1
Physicians			80.5	24.3
Number of night shifts [b]				
All women – total number of night shifts			14.1	12.1
Nurses				
Night shifts of ≤ 8 hours			7.8	7.9
Night shifts of > 8-12 hours			6.6	7.6
Night shifts of > 12 hours			3.9	3.6
Physicians				
Night shifts of ≤ 8 hours			1.1	0.3
Night shifts of > 8-12 hours			1.4	1.9
Night shifts of > 12 hours			8.0	4.6
Weekly working hours – paid and unpaid leave excluded [b]				
All women			23.6	6.7
Nurses			22.9	6.2
Physicians			28.5	6.5
Days of absence – sick leave and pregnancy leave included [b]				
All women			31.6	38.7
Nurses			34.4	38.9
Physicians			15.7	25.9

[a] workers with ≥ 1 day shift and ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks
[b] during the first 32 pregnancy weeks

Nearly 18% of the women in the study cohort had 1-3 days of absence; 17% had 4-7 days and 8-14 days respectively; 13% had 15-28 days and 35% had > 28 days of absence during the first 32 pregnancy weeks (figure 1). Around 33% (N=3 264) of the cohort had at least one period lasting> 14 days. This distribution was similar to that observed among 20 912 pregnant women from the same source population with ≥ 1 shift of any type during the first 32 pregnancy weeks (data not shown). We observed large differences in the duration of periods of pregnancy leave compared to sick leave. Registrations of pregnancy leave lasted on average 44 days (median 33.0, SD 40.3), being 60% of the periods > 14 days, and were observed for half of the study cohort (N=4976), mainly during the 2nd and 3rd trimesters. These women had slightly higher proportion of overweight and obesity, and of medium and low SES compared to the rest of the cohort. Sick leave periods lasted on average 9.1 days (median 6.0, SD 11.9), were equally distributed throughout pregnancy, and only 5% of the periods lasted > 14 days.

Figure 1. Distribution of total days of absence, including sick leave and pregnancy leave, during the first 32 pregnancy weeks among 9799 public hospital employees [a] in Denmark, 2007–2013.
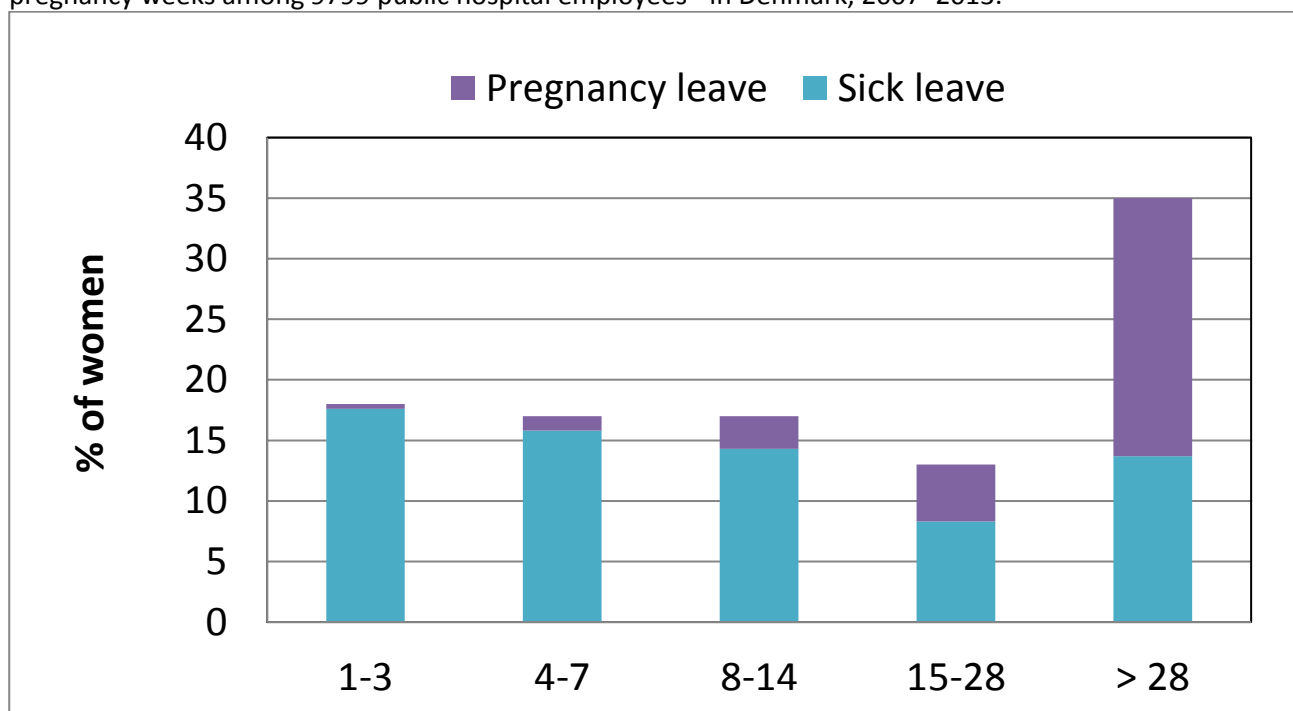
[a] workers with ≥ 1 day shift and ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks

We found increased odds ratio of calling in sick within 24 hours after night versus day shifts in all pregnancy trimesters (OR 1.28, 95% CI 1.19-1.37 in the 1st trimester; OR 1.27, 95% CI 1.17-1.39 in the 2nd trimester; and OR 1.13, 95% CI 0.96-1.31 in the 3rd trimester) – see table 2. Physicians presented the highest estimates (OR 1.94, 95% CI 1.67-2.27; p-value for multiplicative interaction with occupation < 0.0001). Figure 2 presents stratification by pregnancy month for the whole cohort. The overall risk during the first 32 pregnancy weeks was OR 1.23, 95% CI 1.17-1.29.

Table 2. Risk of calling in sick, regardless of duration of sick leave, within 24 hours after night versus day shifts during the first 32 pregnancy weeks with the participants as their own controls [a] among 9799 public hospital employees [b] in Denmark, 2007–2013.

	Risk days (N)	Odds Ratio	95% Confidence Interval
1st pregnancy trimester			
All women	197 851	1.28	1.19-1.37
Nurses (N=6334)	124 091	1.14	1.05-1.24
Physicians (N=1593)	40 252	1.94	1.67-2.27
2nd pregnancy trimester			
All women	182 838	1.27	1.17-1.39
Nurses	111 665	1.02	0.91-1.15
Physicians	40 496	1.89	1.59-2.26
3rd pregnancy trimester			
All women	93 649	1.13	0.96-1.33
Nurses	53 257	1.01	0.81-1.25
Physicians	24 965	1.49	1.09-2.04

[a] fixed effects logistic regression analysis
[b] workers with ≥ 1 day shift and ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks
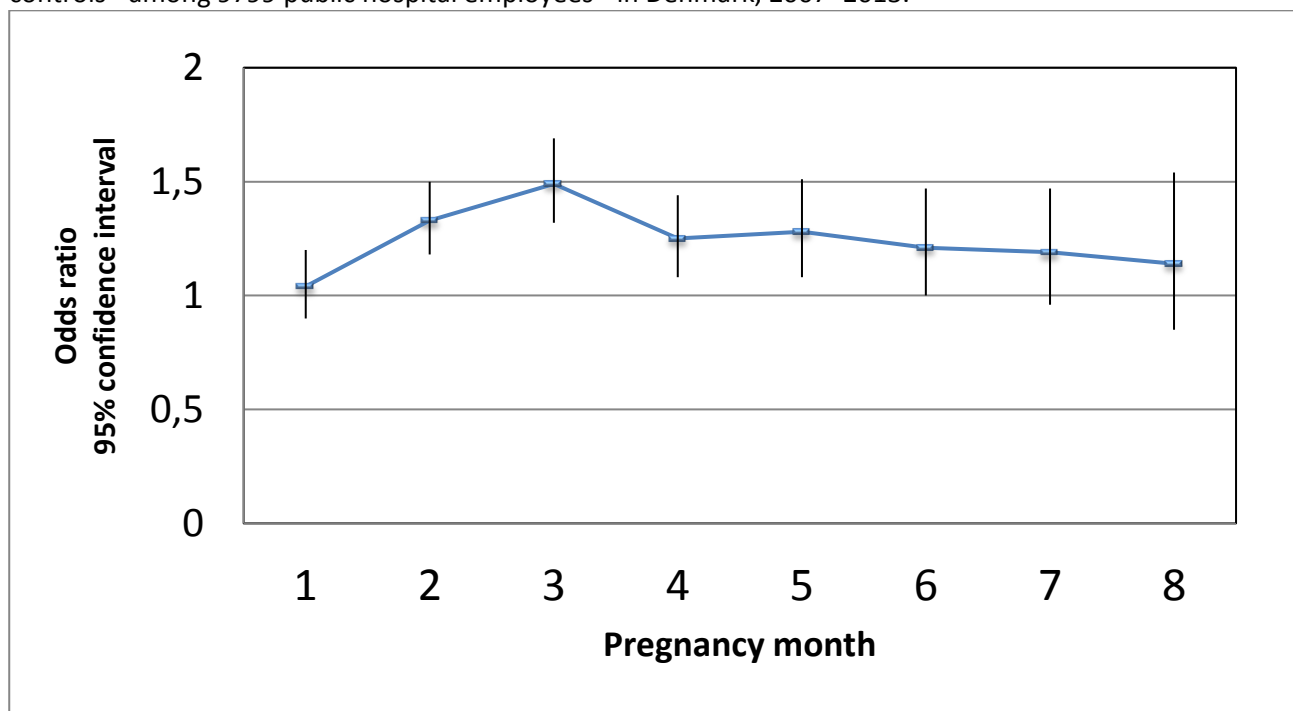
Figure 2 . Risk of calling in sick, regardless of duration of sick leave, within 24 hours after night versus day shifts during the first 32 pregnancy weeks stratified by pregnancy month with the participants as their own controls [a] among 9799 public hospital employees [b] in Denmark, 2007–2013.

[a] fixed effects logistic regression
[b] workers with ≥ 1 day shift and ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks

The association between night shifts and the risk of sick leave was modified by age (p-value for multiplicative interaction 0.03) but not by BMI (p-value for multiplicative interaction 0.32). The OR of sick leave following night shifts was 1.42 (95% CI 1.24-1.63) among women older than 35 years; 1.25 (95% CI 1.17-1.35) among women aged 30-35 years, and 1.16 (95% CI 1.08-1.25) among women younger than 30 years.

The effect of night shifts on the risk of calling in sick within 24 hours following night shifts was driven by night shifts lasting > 12 hours (OR 1.55, 95% CI 1.43-1.69 among all women; OR 1.37, 95% CI 1.15-1.63 among nurses; and OR 1.87, 95% CI 1.69-2.08 among physicians) – see table 3. Analysis of night shifts of ≤ 8 and > 8-12 hours among physicians revealed relatively higher estimates, but they were based on quite few shifts (table 3).

Table 3. Risk of calling in sick, regardless of duration of sick leave, within 24 hours after night shifts of different length compared to day shifts during the first 32 pregnancy weeks with the participants as their own controls [a] among 9799 public hospital employees [b] in Denmark, 2007–2013.

	Risk days (N)	Odds Ratio	95% Confidence Interval
All women	474 338		
Day shifts	391 064	1.00	Reference
Night shifts lasting ≤ 8 hours	35 229	1.20	1.12-1.30
Night shifts lasting > 8-12 hours	28 892	1.02	0.93-1.10
Night shifts lasting > 12 hours	19 153	1.55	1.43-1.69
Nurses (N=6334)	289 013		
Day shifts	233 194	1.00	Reference
Night shifts lasting ≤ 8 hours	28 629	1.06	0.97-1.16
Night shifts lasting > 8-12 hours	23 254	1.00	0.91-1.10
Night shifts lasting > 12 hours	3936	1.37	1.15-1.63
Physicians (N=1593)	105 713		
Day shifts	93 156	1.00	Reference
Night shifts lasting ≤ 8 hours	15	2.32	0.30-18.20
Night shifts lasting > 8-12 hours	87	3.10	1.40-6.87
Night shifts lasting > 12 hours	12 455	1.87	1.69-2.08

[a] workers with ≥ 1 day shift and ≥ 1 night shift and ≥ 1 day of sick leave during the first 32 pregnancy weeks
[b] fixed effects logistic regression analysis

Sensitivity analyses either restricted to nulliparous women (N=5095) or with both sick leave and pregnancy leave as the outcome slightly attenuated the estimates, mainly during the 2nd and 3rd trimesters (data not shown), but the effects observed in the main analyses remained.

DISCUSSION

This is to our knowledge the first study of the acute effect of night work on sick leave during pregnancy presenting trimester-specific estimates and applying a statistical method that accounts for personal and time-invariant factors. We found that night shifts, especially long shifts, are a risk factor for calling in sick within 24 hours after the shift in all pregnancy trimesters.

Our findings are in accordance with prior Danish studies showing an increased risk of sick leave during pregnancy among shift workers (1, 5, 8). Similar to our cohort, Kaerlev and colleagues investigated hospital employees (N=773) (8). They used roster data on job tasks and sick leave, and questionnaire information on working schedules. They found that night or shift work was a risk factor for sick leave corresponding to > 10% of the scheduled work time (OR 1.4, 95%CI 1.0-1.9 adjusted for age, occupation, full- or part-time job and previous sick leave). Using data from the Danish National Birth Cohort from 1996 to 2002, Hansen et al. investigated occupational exposures in relation to sick leave during pregnancy among 51 874 women (5). They included primarily sick leave periods of > 15 days from the Danish Register for Evaluation of Marginalisation (DREAM). Information on working schedules was based on an interview conducted between 17 and 30 pregnancy weeks. They found an increased risk of sick leave among women with shift work including night shifts (hazard ratio 1.61, 95% CI 1.42-1.83), and a trend of increasing risk with increasing number of monthly night shifts (HR 1.89, 95% CI 1.67-2.15 among women with > 8 night shifts per pregnancy month). Lastly, sick leave of > 20 days was reported more frequently by women who worked evening and/or night shifts during pregnancy in a survey of 508 women (1).

The rate of 33% of the women in this cohort having at least one period of absence lasting > 14 days is also in line with prior Scandinavian studies (1, 2, 5, 7, 8). However, considering that our cohort did not include women on sick leave throughout pregnancy, neither those with fixed night, fixed evening or fixed day shifts, it is possible that this rate is underestimated.

Our findings of higher risk of sick leave following night shifts during 1st trimester may be partly explained by selection out of night work, into either other working schedules or into long-term sick leave, by women experiencing pregnancy complications. Such a change of working schedules happens usually during the end of the 1st trimester, when many Danish women inform their workplace about their pregnancy. Figure 2 illustrates this by the increasing relative risk of calling in sick within 24 hours after night shifts during the 1st trimester followed by a relative decrease during the 2nd and 3rd trimester. It is important to notice that we did not investigate the cumulative risk of sick leave during pregnancy. Our analyses included only women who were at work and had a change of both exposure (≥ 1 day shift and ≥ 1 night shift) and outcome (≥ 1 day of sick leave) in the respective pregnancy trimester. As rates of sick leave are known to increase throughout pregnancy (6, 8), women who continue working night shifts until the 3rd trimester are probably healthier (28). It was therefore not surprising that the risk of calling in sick after a night shift in our study was higher in the 1st pregnancy trimester, i.e. before the healthy worker selection has occurred. Nevertheless, even women who worked night shifts until the 3rd trimester (N=8382), in our cohort, were at increased risk of sick leave after a night shift. This is, probably, because night work at this point may add to

the effects of insufficient sleep and fatigue physiologically imposed by late pregnancy. It is also important to keep in mind that sick leave during pregnancy in relation to night work might also be associated with other potentially more severe disorders than fatigue (22, 29-33).

Analysis restricted to nulliparous women revealed attenuated estimates. It is known that first time pregnancies are at increased risk of certain complications, such as hypertensive disorders (34). However, women who experienced complications in prior pregnancies might be more cautious and hereby have a lower threshold to call in sick in subsequent pregnancies.

We also observed attenuation of the estimates in analysis including pregnancy leave as the outcome. This was not surprising, as pregnancy leave in our cohort represented mostly medical complications requiring planned and long-term absence. The longer duration of pregnancy leave periods might have contributed to the healthy worker effect later in pregnancy. This is supported by the almost identical results for the 1st trimester for sensitivity analysis including pregnancy leave (OR 1.27, 95% CI 1.19-1.35) and main analysis (OR 1.28, 95% CI 1.19-1.37 – from table 1), but attenuation of the estimates in the 2nd and 3rd trimesters.

Shift's characteristics

We found that occupation modified the effect of night work on sick leave. Even though we pursued to disentangle the different dimensions of night work for research purposes, what we observed is a combination of them. The different results observed among nurses and physicians in our cohort might partly be explained by differences in absence rates in and in the organization of shift work. Nurses had higher rates of absence (see table 1), especially during the 1st trimester, and higher proportion of absence periods lasting > 14 days (46%) and > 28 days (31%) compared to physicians (27% and 16%, respectively). Consequently, relatively more physicians than nurses contributed to analyses of the 2nd and 3rd trimesters. Furthermore, in Denmark, while nurses tend to have regular 3-shifts schedules, physicians have almost exclusively night shifts longer than 12 hours (26, 27). Even though physicians have the possibility of on-call shifts and planned sleeping breaks more frequently than nurses, emergency duties across departments may limit this possibility in praxis. This combined effect of long night shifts and increased workload might aggravate fatigue and insufficient recovery explaining the relatively higher estimates among physicians.

Similarly, the combination of long night shifts with increased workload might explain the effect of night shifts > 12 hours on the risk of calling in sick within 24 hours observed for nurses (table 3). Among them, long night shifts occurred mostly when they worked two shifts in a row. Such changes in working schedules reflect frequently increased workload due to, for example, sick leave among colleagues or increased number of patients in a hospital department.

The design of our study was not appropriate to investigate consecutive night shifts and quick returns but they have been negatively associated with several health outcomes (35, 36), and may also contribute to the effect of night work on sick leave during pregnancy. In a recent published study using the same source population as in the present study, we found that women with longer spells of consecutive night shifts, and among obese women also those with long night shifts and quick returns, during the first 20 pregnancy weeks had increased risk of hypertensive disorders (22). Field studies have shown increasing hormonal dysfunction with increasing number of consecutive night shifts (37-39). Additionally, most of the workers in our cohort have irregularly rotating shifts and do not fulfil the suggested recommendation of at least two days off following a night shift to adjust the circadian rhythm back to a day pattern (40).

Strengths and limitations

The large sample size, objective and detailed exposure assessment, prospective design, and the use of the workers as their own controls are the major strengths of our study. Selection bias due to incomplete coverage was reduced to a minimum due to the nationwide source population. Adequate comparisons of sick leave between individuals is challenging because sick leave is highly correlated with personal factors, such as prior health, threshold for calling in sick, and family and work environment (4). The use of within-workers comparisons fully account for personal factors and time-invariant confounders. This design has been shown as efficient in other studies of occupational exposures (14). However, fixed effects modelling does not account for time-variant factors, such as work content. This might have induced bias towards the null in our cohort because work tasks vary largely from day-to-day in a hospital, and fatigue is presumably higher following night shifts with increased workload.

Our results are based on a cohort of hospital employees with the majority having unregularly changing schedules nearly weekly. Therefore, our results may not apply for populations with other working schedules. Not including pregnancy leave in the main analysis, may have isolated the effect of working schedules on sick leave independently of pregnancy complications. Although, whether our results apply for non-pregnant women with similar working schedules, waits to be proven.

CONCLUSION

Among Danish public hospital employees night shifts during pregnancy, especially shifts longer than 12 hours, increased the risk of calling in sick the following day independent of personal factors and time-invariant confounders in all pregnancy trimesters. If pregnant women work at night, reducing the frequency and duration of night shifts in the organization of their working schedules may reduce sick leave during pregnancy.

CONTRIBUTORSHIP

Paula E. C. Hammer, Jens P. Bonde, Anne H. Garde, Esben M. Flachs, Ann D. Larsen and Luise M. Begtrup provided substantial contributions to the conception of the study and the analysis of the data. Paula E. C. Hammer, Anne H. Garde, Ann D. Larsen contributed to the acquisition of the data. Paula E. C. Hammer was responsible for drafting the paper. All authors contributed substantially to the interpretation of the data, the critical revision of the paper for important intellectual content, and the final approval of the version published. All authors are accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no conflicts of interest.

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Paper III (submitted to the Scandinavian Journal of Work, Environment and Health, November 2018)

Night work and severe postpartum depression: a national register-based cohort study

Hammer PEC, Hageman I, Garde AH, Begtrup LM, Flachs EM, Hansen J, Hansen ÅM, Hougaard KS, Kolstad HA, Larsen AD, Pinborg AB, Specht IO, Bonde JP.

NIGHT WORK AND POSTPARTUM DEPRESSION:

A NATIONAL REGISTER-BASED COHORT STUDY

Paula E C Hammer[1], Ida Hageman[2], Anne H Garde[3,4], Luise M Begtrup[1], Esben M Flachs[1], Johnni Hansen[5], Åse M Hansen[3,4], Karin S Hougaard[3,4], Henrik A Kolstad[6], Ann D Larsen[3], Anja Pinborg[7], Ina O Specht[8], Jens Peter Bonde[1,4]

[1] Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark.

[2] Mental Health Services, Capital Region of Denmark, Copenhagen University Hospital, Copenhagen, Denmark.

[3] National Research Centre for the Working Environment, Copenhagen, Denmark.

[4] University of Copenhagen, Department of Public Health, Copenhagen, Denmark.

[5] Danish Cancer Society Research Centre, Copenhagen, Denmark.

[6] Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark.

[7] Fertility Clinic, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark.

[8] The Parker Institute, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark.

Corresponding author

Paula Edeusa Cristina Hammer

Bispebjerg Bakke 23, indgang 20F - 2400 Copenhagen, Denmark

e-mail: paulahammer@dadlnet.dk

Telephone: +45 38 63 61 72 Mobile: +45 51 23 74 35 Fax: +45 38 63 61 72

ABSTRACT

Objective

We aimed to investigate the association of night work during pregnancy with the risk of severe postpartum depression (PPD).

Methods

We performed a nationwide register-based cohort study of workers in the five Danish public hospital employees. Daily information on working hours was retrieved from The Danish Working Hour Database from January 2007 to December 2015. Pregnancies, covariates and outcome were identified from National registries for births and hospital contacts. We performed logistic regression of the risk of PPD in relation to number and duration of night shifts, spells of consecutive night shifts, and short shift intervals during the first 32 pregnancy weeks adjusted for age, body mass index, socioeconomic status, parity, sickness absence three months prior to pregnancy and prior diagnosed severe depression.

Results

The study cohort comprised 25 009 singleton pregnancies from 19 382 workers. The majority were nurses (45%) or physicians (13%). Overall, we did not observe an increased risk of PPD for any of the dimensions of night work analyzed. We found, however, an increased risk of PPD (adjusted odds ratio 2.08 95% confidence interval 1.09-4.00) among women who stopped working night shifts after the first pregnancy trimester (N=3094).

Conclusion

Overall, our results do not support night work during pregnancy as a risk factor for severe PPD among. However, we observed a 2-fold increased risk of PPD among women who stopped working night shifts after the first pregnancy trimester. This may reflect the influence of the healthy worker survivor effect and warrants further attention.

INTRODUCTION

The prevalence of postpartum depression (PPD) is estimated to 10-15%, but considerably higher rates have been reported across countries (2). Postpartum depression imposes potential severe consequences to mother, child, family and the society, being one of the primary causes of maternal mortality in many countries (3, 4). It has therefore been considered a global public health problem (5).

The pathogenesis of PPD is complex and multifactorial involving endocrine, genetic and environmental factors (2, 6). The strongest known risk factors for PPD are prior own or family history of major depressive disorder (2, 6, 7). Other factors shown to be related with the development of PPD are adverse life events, inadequate social support and low socioeconomic status (SES) (8-10). Identification of potentially modifiable risk factors for PPD is crucial for prevention.

A recent systematic review of 11 longitudinal studies on night work and the risk of depression performed a meta-analysis of the five studies with observation periods of ≥ 2 years revealing some indication of an increased risk of depression among night workers (risk estimate 1.42, 95% CI 0.92-2.19) (11). Another similar systematic review also including 11 studies used different inclusion criteria, and therefore only three studies contributed to both reviews, being the eight remaining studies of cross-sectional design. They found that night work was associated with an increased risk of depression (relative risk 1.43, 95% CI 1.24-1.64) across sex, night work duration, type of occupation, continent and type of publication (12). These reviews did not inform whether PPD was included in any of the studies. As pointed out by Angerer and colleagues (11), prior studies on depression in relation to night work are challenged by cross-sectional design, self-reported exposure and outcome, and the possibility of the healthy worker survivor effect, i.e. the selection of individuals with poorer health status out of night work (13, 14).

Night work is common among women in the reproductive age. In 2016 around 14% of the female European workers under the age of 50 years engaged in night work (15). The mechanisms linking night work to the risk of PPD are suggested to involve hormonal dysfunction, inflammation and sleep disorders (16-25). Especially sleep disorders are of importance because they add to the physiological sleep disturbances imposed by pregnancy (25).

We aimed to investigate the association of different dimensions of night work, expressed by frequency and duration of night shifts throughout pregnancy, with the risk of severe PPD. The novel aspect of our study is the use of clinically diagnosed outcome and objective information on pregnancy period-specific exposure.

METHODS

Design

Similar to our previously published study (26) we conducted a prospective register-based cohort study with information from the following Danish national registries linked on individual level through the civil registration number: 1) The Danish Working Hour Database (DWHD), a national payroll database covering more than 250 000 employees in the Danish administrative regions including all public hospital employees from January 2007 to December 2015 (27); 2) The Danish Medical Birth Registry, which contains information from all births in Denmark since 1973 (28); 3) The Danish National Patient Registry, which contains data on hospital admissions since 1977 and on outpatients since 1994 (29); and 4) The Danish Psychiatric Central Research Registry, providing information on psychiatric inpatient treatment since 1969 and on outpatient treatment since 1995 (30).

Cohort

The source population were women from the DWHD who gave birth at least once between 2007 and 2015 (N=43 833 women with 70 306 births). We excluded women ≤ 18 and ≥ 50 years (N=16 pregnancies); multiple pregnancies (N=3243); pregnancies resulting in still births (N=254); pregnancies conceived in 2006 (N=6383), because they lacked payroll data from conception to January 2007; and pregnancies without at least one day or night shift during the first 32 pregnancy weeks (N=4954). To ensure that payroll data was available throughout the first 32 pregnancy weeks, we excluded pregnancies with employment in one the administrative regions of Denmark, i.e. registration in the DWHD, starting after conception or ending before 32 pregnancy weeks (N=25 330). Finally, we excluded pregnancies with other working schedules than fixed day shifts or at least one night shift during the first 32 pregnancy weeks (N=5117), for example fixed evening shifts, leaving 25 009 singleton pregnancies from 19 382 women eligible for analysis (figure 1).

Figure 1. Flowchart for identification of the study population.

265 898 employees in public administration and hospitals in Denmark from the Danish Working Hour Database

70 306 pregnancies from 43 833 women identified from the Medical Birth Registry with at least one birth between January 2007 and December 2015

Excluded:

Age < 18 and > 50 years old (N=16 pregnancies)

Multiple pregnancies (N=3243)

Still births (N=254)

Conception in 2006 (N=6383)

No day or night shift during the first 32 pregnancy weeks (N=4954)

Pregnancies with employment in one the administrative regions of Denmark starting after conception or ending before 32 pregnancy weeks weeks (N=25 330)

Other working schedules than fixed day shifts or ≥ 1 night shift during the first 32 pregnancy weeks (N=5117)

25 009 singleton pregnancies from 19 382 women eligible

Exposure

The DWHD provided daily information on exact time of start and end of all workdays and all types of paid and unpaid leave, job title and place of employment. Shifts during the first 32 pregnancy weeks, including on-call shifts, lasting ≥ 3 hours were defined as day (start time after 06:00 and end time before 21:00) or night shifts (any start and end time including any duration of working hours between 23:00 and 06:00). They corresponded to 84 % of all registered shifts, the rest being early morning or evening shifts. We applied the cut-off of 32 pregnancy weeks because workers in the Danish administrative regions are entitled to pregnancy leave eight weeks prior to their due date. The different dimensions of night work were expressed by number and duration of night shifts, consecutive night shifts and quick returns as defined below.

Number of night shifts. The cumulated number of night shifts during the first 32 pregnancy weeks was categorized as 0 (fixed day work), 1-8, or ≥ 9 night shifts (roughly corresponding to more than one night shift per pregnancy month on average).

Duration of night shifts. The duration of night shifts was defined as ≤ 8 hours, > 8-12 hours or > 12 hours (long night shifts). The categories used for analysis were either working only night shifts ≤ 8 hours or at least one night shift of > 12 hours during the first 32 pregnancy weeks.

Consecutive night shifts. Categories of consecutive night shifts were 1 (only single night shifts), 2-3 (at least one spell of 2-3 consecutive night shifts and no spells of ≥ 4 consecutive night shifts), or ≥ 4 (at least one spell of ≥ 4 consecutive night shifts) during the first 32 pregnancy weeks.

Quick returns. We defined quick returns as intervals of < 11 hours between any type of shifts according to the European Union's Working Time Directive (31), or of < 28 hours after a night shift, as suggested by a prior study using payroll data (32). The cumulated number of quick returns during the first 32 pregnancy weeks was categorized as 0, 1-8 or ≥ 9 quick returns (roughly corresponded to more than one quick return per pregnancy month on average).

Reference group. In all analyses we used two reference groups, fixed day work for comparisons of night versus day work, and the lowest category of exposure for within night work comparisons.

Outcome

The outcome PPD was identified by ICD-8 (296.0 – involutional melancholia and 300.4 – depressive neurosis) or ICD-10 (F32 – depressive episode and F33 – recurrent depressive disorder) codes registered as

the primary diagnose at somatic or psychiatric hospital departments either as in- or outpatient treatment. As most of the women with perinatal psychiatric disorders in Denmark are treated in primary care (33), the outcome of our study was severe depression requiring in- and/or outpatient treatment at a hospital. The dates of registration were classified as prior (from 1969 to conception date) or postpartum (from birth to one year postpartum) in relation to each pregnancy.

Covariates

Covariates were chosen a priori based on data availability and previous literature (2, 8, 34, 35).

Age (<30, 30-35, >35 years), BMI (<25, 25.0-29.9, ≥ 30 kg/m^2) and parity (1, 2, ≥ 3) registered by the midwife or family doctor at the first antenatal visit derived from The Danish Medical Birth Registry. The classification of SES into high, low or medium derived from Statistics Denmark and was based on the two Danish versions of the International Standard Classification of Occupations from 2007-2009 and 2010-2015 (ISCO-88 and ISCO-08), respectively (36, 37). Sickness absence three months prior to pregnancy (0, 1-9 or ≥ 10 days) expressed the sum of all days registered with at least three hours of sickness absence in DWHD during this period. Prior diagnosed severe depression (yes/no) derived from The Danish National Patient Registry and The Danish Psychiatric Central Research Registry as outlined above.

Statistical Analysis

We performed logistic regression of the risk of PPD by different dimensions of night work during the first 32 pregnancy weeks. We applied generalized estimating equations to account for repeated pregnancies within participants. We presented crude and adjusted estimates as odds ratio (OR) with 95% confidence interval (CI). Adjusted analyses included categories of age, BMI, SES, parity, sickness absence three months prior to pregnancy and prior diagnosed severe depression.

We performed the following sensitivity analyses: 1) restricted to nulliparous women; 2) restricted to nurses, who represented most of the cohort; 3) restricted to pregnancies without prior diagnosed severe depression; and 4) within-night work analysis with restriction to night work during the first or first and second trimester compared to night work throughout pregnancy. The reason for the latter was to evaluate the potential presence of healthy worker survivor effect in the main analysis. In another words, the possibility of women somehow susceptible to PPD stop working night shifts during pregnancy and, therefore, not contributing to the group of workers with the highest cumulated exposure to night work.

We used a significance level of 0.05. The analyses were done with SAS 9.4 software (SAS Institute, Cary, North Carolina, United States).

RESULTS

The study cohort comprised 25 009 singleton pregnancies from 19 382 women. Their personal and working time characteristics are presented in table 1. Most of the night workers were nurses (64%) or physicians (17%), while most of the day workers were medical secretaries (18%), nurses (15%) and physiotherapists (14%). In only 84 (0.3%) pregnancies the working schedule was fixed night shifts. Night workers had on average 14.5 night shifts during the first 32 pregnancy weeks. Around 39% of night shifts lasted ≤ 8 hours, 32% lasted 9-12 hours and 29% > 12 hours. Women who worked at least one spell of ≥ 4 consecutive night shifts had considerably higher number of consecutive night shifts in total (mean 5.3) compared to those with spells of 2-3 and no spells of ≥ 4 consecutive night shifts (mean 17.7). These categories represented therefore both length of spells and total number of consecutive night shifts. Even though quick returns after a night shift (shift intervals < 28 hours) accounted for the compulsory day off following a night shift, they were more frequent than quick returns between any type of shifts (< 11 hours) – see table 1.

We identified 80 cases of PPD (0.3%) and 427 cases of prior diagnosed severe depression (1.7%). Approximately 20% of the women who developed PPD had a prior diagnose of severe depression, compared to 2% among women who did not develop PPD. Among women with prior diagnosed severe depression 4% developed PPD compared to 0.3% among those without a prior diagnosed severe depression.

Table 1. Characteristics of 25 009 singleton pregnancies among 19 382 public hospital employees in Denmark, 2007–2015.

	Day work [a] (N = 9642)				Night work [b] (N = 15 367)			
	N	%	Mean	SD	N	%	Mean	SD
Age, years			32.3	4.0			31.2	3.8
Body Mass Index, kg/m^2			23.9	6.6			23.9	7.6
Parity								
1	3128	32.9			6204	40.8		
2	4402	46.2			6169	40.5		
≥ 3	1990	20.9			2841	18.7		
Socioeconomic status								
High	2393	25.1			3541	23.1		
Medium	5390	56.6			10 818	70.7		
Low	1741	18.3			948	6.2		
Most frequent occupations								
Laboratory technician	709	7.4			395	2.6		
Medical secretary	1785	18.5			92	0.6		
Nurse	1447	15.0			9842	64.0		
Nurse assistant	279	2.9			801	5.2		
Physician	744	7.7			2654	17.3		
Physiotherapist	1358	14.1			44	0.3		
Psychologist	683	7.1			4	0.03		
Type and number of shifts [c]								
Day			107.4	30.0			60.6	26.7
Early morning			0	0			0.04	0.9
Evening			0	0			13.5	13.9
Night			0	0			14.5	12.5
≤ 8 hours			0	0			5.7	10.3
9-12 hours			0	0			5.0	9.4
> 12 hours			0	0			3.8	7.0
Spells of 2-3 night shifts [d]			0	0			5.3	4.5
Spells of ≥ 4 night shifts [e]			0	0			17.7	11.4
Quick returns			0	0			3.2	4.1
Quick returns after a night shift			0	0			7.9	8.5
Weekly working hours [e]			24.1	7.2			23.5	7.1
Sickness absence three months prior to pregnancy, days			2.9	7.0			2.6	5.4

[a] At least one day shift and no night, evening or early morning shift during the first 32 pregnancy weeks;
[b] At least one night shift during the first 32 pregnancy weeks; [c] During the first 32 pregnancy weeks;
[d] At least one spell of 2-3 and no spells of ≥ 4 consecutive night shifts during the first 32 pregnancy weeks;
[e] At least one spell of ≥ 4 consecutive night shifts; [f] Paid and unpaid leave excluded

Table 2 shows the results for the analysis of number of night shifts. Adjusted OR for PPD among women who worked ≥ 9 night shifts during the first 32 pregnancy weeks was 0.59 (95% CI 0.33-1.06) compared to day work and 0.66 (95% CI 0.36-1.23) compared to having 1-8 night shifts.

The results for the analysis of duration of night shifts are presented in table 3. Adjusted OR for PPD among women who worked long night shifts (> 12 hours) was 0.71 (95% CI 0.38-1.36) compared to day work and 0.76 (95% CI 0.29-1.97) compared to working only night shifts lasting ≤ 8 hours.

Table 4 presents the results for number of consecutive night shifts. Adjusted OR for PPD among women who worked ≥ 4 consecutive night shifts weeks was 0.54 (95% CI 0.22-1.30) compared to day work and 0.69 (95% CI 0.23-2.08) compared to working only single night shifts.

Table 5 presents the results for quick returns. Adjusted OR for PPD among women who worked with ≥ 9 quick returns was 0.75 (95% CI 0.26-2.18) compared to day work, and 0.76 (95% CI 0.24-2.38) compared to night work without quick return. Adjusted OR for PPD among pregnancies with ≥ 9 quick returns after a night shift was 0.57 (95% CI 0.27-1.19) compared to day work, and 0.29 (95% CI 0.11-0.72) compared to nigh work without quick return after a night shift.

Table 2. Odds ratios of postpartum depression by number of night shifts during the first 32 pregnancy weeks among 19 382 public hospital employees in Denmark, 2007–2015.

Number of night shifts	Pregnancies		Cases		Crude analysis		Adjusted analysis [a]	
	N	%	N	%	OR	95% CI	OR	95% CI
All pregnancies, N=25 009								
Day work [b]	9642	38.5	36	0.4	1.00	Referent	1.00	Referent
1-8	5827	23.3	23	0.4	1.06	0.62-1.81	0.89	0.50-1.58
≥ 9	9540	38.2	21	0.2	0.59	0.34-1.02	0.59	0.33-1.06
P for trend					0.06		0.08	
Pregnancies with ≥ 1 night shift during the first 32 pregnancy weeks, N=15 367								
1-8	5827	37.9	23	0.4	1.00	Referent	1.00	Referent
≥ 9	9540	62.1	21	0.2	0.56	0.31-1.01	0.66	0.36-1.23

OR = odds ratio; CI = confidence interval
[a] Adjusted for age, body mass index, socioeconomic status, parity, sickness absence three months prior to pregnancy and prior diagnosed severe depression
[b] At least one day shift and no night, evening or early morning shift during the first 32 pregnancy weeks

Table 3. Odds ratios of postpartum depression by duration of night shifts during the first 32 pregnancy weeks among 19 382 public hospital employees in Denmark, 2007–2015.

Duration of night shifts	Pregnancies		Cases		Crude analysis		Adjusted analysis [a]	
	N	%	N	%	OR	95% CI	OR	95% CI
All pregnancies, N=19 125								
Day work [b]	9642	50.4	36	0.4	1.00	Referent	1.00	Referent
≤ 8 hours [c]	3427	17.9	10	0.3	0.78	0.38-1.59	0.74	0.35-1.55
> 12 hours [d]	6056	31.7	17	0.3	0.75	0.42-1.35	0.71	0.38-1.36
P for trend					0.31		0.26	
Pregnancies with ≥ 1 night shift during the first 32 pregnancy weeks, N=9 483								
≤ 8 hours	3427	36.1	10	0.3	1.00	Referent	1.00	Referent
> 12 hours	6056	63.9	17	0.3	0.96	0.44-2.10	0.76	0.29-1.97

OR = odds ratio; CI = confidence interval
[a] Adjusted for age, body mass index, socioeconomic status, parity, sickness absence three months prior to pregnancy and prior diagnosed severe depression.
[b] At least one day shift and no night, evening or early morning shift during the first 32 pregnancy weeks.
[c] Only night shifts lasting ≤ 8 hours
[d] At least one night shift lasting > 12 hours

Table 4. Odds ratios of postpartum depression by consecutive night shifts during the first 32 pregnancy weeks among 19 382 public hospital employees in Denmark, 2007–2015.

Consecutive night shifts	Pregnancies		Cases		Crude analysis		Adjusted analysis [a]	
	N	%	N	%	OR	95% CI	OR	95% CI
All pregnancies, N=25 009								
Day work [b]	9642	38.5	36	0.4	1.00	Referent	1.00	Referent
1 [c]	5172	20.7	18	0.4	0.93	0.52-1.66	0.93	0.49-1.77
2-3	7409	29.7	20	0.3	0.72	0.41-1.26	0.63	0.35-1.16
≥ 4	2786	11.1	6	0.2	0.58	0.24-1.38	0.54	0.22-1.30
P for trend						0.12		0.08
Pregnancies with ≥ 1 night shift during the first 32 pregnancy weeks, N=15 367								
1	5172	33.7	18	0.4	1.00	Referent	1.00	Referent
2-3	7409	48.2	20	0.3	0.78	0.41-1.47	0.79	0.35-1.80
≥ 4	2786	18.1	6	0.2	0.62	0.25-1.56	0.69	0.23-2.08
P for trend						0.26		0.50

OR = odds ratio; CI = confidence interval
[a] Adjusted age, body mass index, socioeconomic status, parity, sickness absence three months prior to pregnancy and prior diagnosed severe depression
[b] At least one day shift and no night, evening or early morning shift during the first 32 pregnancy weeks
[c] Only single night shifts

Table 5. Odds ratios of postpartum depression by number of quick returns [a] and quick returns after a night shift [b] during the first 32 pregnancy weeks among 19 382 public hospital employees in Denmark, 2007–2015.

Quick Returns	Pregnancies		Cases		Crude analysis		Adjusted analysis [c]	
	N	%	N	%	OR	95% CI	OR	95% CI
All pregnancies, N=25 009								
Day work [d]	9642	38.5	36	0.4	1.00	Referent	1.00	Referent
0 [e]	4605	18.4	19	0.4	1.11	0.63-1.95	1.05	0.57-1.93
1-8	9274	37.1	21	0.2	0.61	0.35-1.05	0.54	0.30-0.96
≥ 9	1488	6.0	4	0.3	0.72	0.25-2.03	0.75	0.26-2.18
P for trend					0.09		0.07	
Pregnancies with ≥ 1 night shift during the first 32 pregnancy weeks, N=15 367								
0	4605	30.0	19	0.4	1.00	Referent	1.00	Referent
1-8	9274	60.3	21	0.2	0.55	0.29-1.02	0.54	0.27-1.08
≥ 9	1488	9.7	4	0.3	0.65	0.22-1.91	0.76	0.24-2.38
P for trend					0.16		0.30	
Quick Returns after a night shift								
All pregnancies, N=25 009								
Day work	9642	38.5	36	0.4	1.00	Referent	1.00	Referent
0	1078	4.3	8	0.7	2.00	0.92-4.33	1.99	0.89-4.48
1-8	9159	36.6	25	0.3	0.73	0.43-1.23	0.63	0.36-1.09
≥ 9	5130	20.5	11	0.2	0.57	0.29-1.14	0.57	0.27-1.19
P for trend					0.06		0.04	
Pregnancies with ≥ 1 night shift during the first 32 pregnancy weeks, N=15 367								
0	1078	7.0	8	0.7	1.00	Referent	1.00	Referent
1-8	9159	59.6	25	0.3	0.37	0.16-0.81	0.29	0.13-0.66
≥ 9	5130	33.4	11	0.2	0.29	0.12-0.72	0.29	0.11-0.72
P for trend					0.06		0.10	

OR = odds ratio; CI = confidence interval
[a] Less than 11 hours between any type of shifts
[b] Less than 28 hours between a night shift and the next shift
[c] Adjusted for age, body mass index, socioeconomic status, parity, sickness absence three months prior to pregnancy and prior diagnosed severe depression
[d] At least one day shift and no night, evening or early morning shift during the first 32 pregnancy weeks
[e] At least one night shift and no quick returns

Sensitivity Analyses

Sensitivity analysis restricted to nulliparous women (N=9332) did not substantially change the results from the main analyses (results not shown).

Analysis restricted to pregnancies without prior diagnosed severe depression (N=24 582) revealed adjusted OR 0.60 (95% CI 0.33-1.11) for women who worked ≥ 9 night shifts; OR 0.61 (95% CI 0.30-1.25) for women who worked long night shifts; OR 0.57 (95% CI 0.22-1.47) for women who worked ≥ 4 consecutive night shifts; OR 0.42 (95% CI 0.10-1.75) for women who worked ≥ 9 quick returns; and OR 0.59 (95% CI 0.28-1.28) for women who worked ≥ 9 quick returns after a night shift.

Analysis restricted to nurses (N=11 298) tended to an increased risk of PPD among women in the lowest categories of exposure compared with day work (adjusted OR 1.49, 95% CI 0.44-5.04 for 1-8 night shifts; OR 1.12, 95% CI 0.31-4.05 for night shifts of ≤ 8 hours; OR 1.27, 95% CI 0.31-5.10 for night work without consecutive night shifts; OR 1.56, 95% CI 0.42-5.82 for night work without quick returns; and OR 1.25, 95% CI 0.22-6.97 for night work without quick returns after a night shift).

Within-night work sensitivity analysis revealed that women who stopped working night shifts after the first trimester (N=3094) presented with an increased risk of PPD (adjusted OR 2.08 95% CI 1.09-4.00) compared to women who worked night shifts throughout pregnancy – see figure 2. The risk of PPD was not increased (adjusted OR 0.79, 95% CI 0.35-1.80) among women who stopped working night shifts after the second trimester (N=5325). Women who stopped working night shifts after the first trimester had lower proportion of high SES (14% versus 25%) but had otherwise similar demographic characteristics as women with night work throughout pregnancy. Both groups had also similar prevalence of prior diagnosed severe depression (1.8 and 1.5% respectively).

Figure 2 – Odds ratios of postpartum depression by night work [a] during the first and second pregnancy trimester compared to night work throughout [b] pregnancy among 19 382 public hospital employees in Denmark, 2007–2015.
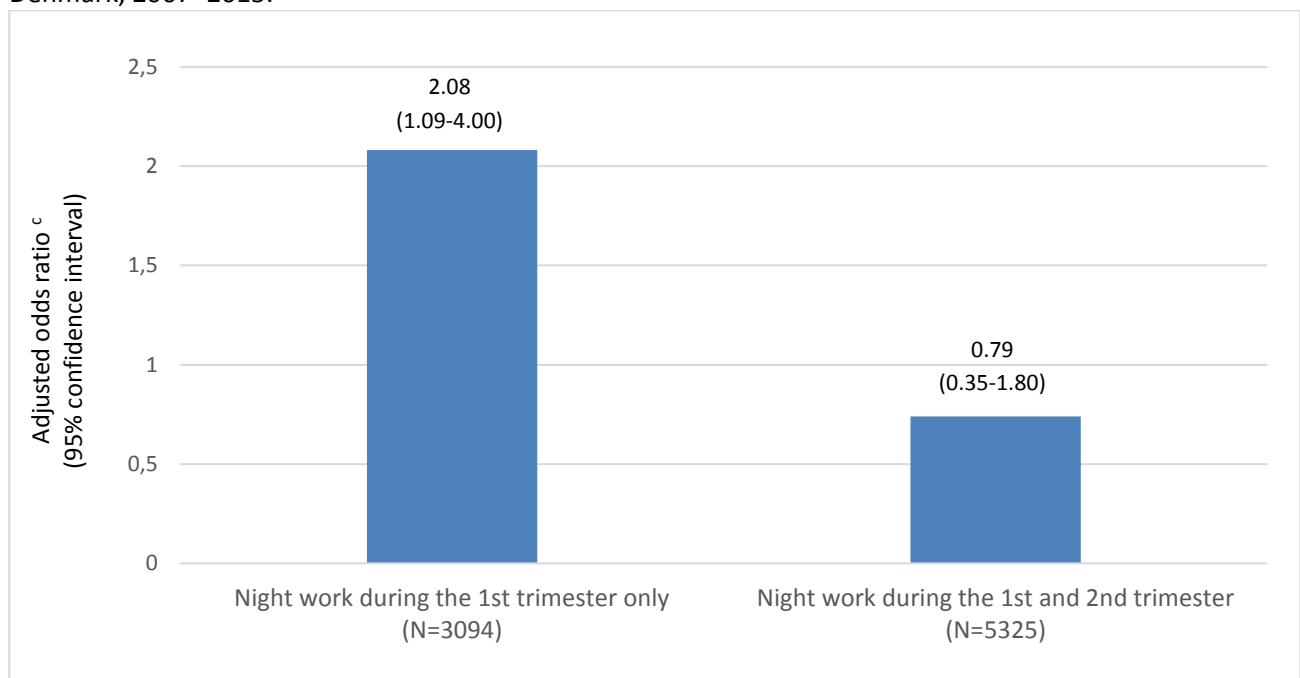
[a] At least one night shift
[b] At least one night shift in each pregnancy trimester up to 32 pregnancy weeks
[c] Adjusted for age, body mass index, socioeconomic status, parity, sickness absence three months prior to pregnancy and prior diagnosed severe depression

DISCUSSION

Overall, we did not find an increased risk of severe PPD in relation to night work during pregnancy in this nationwide cohort of Danish public hospital employees. We found, however, a 2-fold increased risk of PPD among women who stopped working night shifts after the first trimester.

This is, to our knowledge, the first study investigating the association between different dimensions of night work during pregnancy and the risk of severe PPD. Prior longitudinal studies of the association between night work and depression among hospital employees found inconsistent results – four found positive association (38-41) and two found no association (42, 43). The two studies, which similarly to our study, accounted for changes of working schedules found that selection out of night work masked an effect of night work on the risk of common mental disorders (OR 1.25, 95% CI 1.03-1.52) (41) and of anxiety and depressive symptoms (no risk estimates informed) (40). Direct comparisons are though not possible as

these studies applied self-reported information on depressive symptoms, not clinically diagnosed depression, and crude assessed exposure.

The lack of association between PPD and the different dimensions of night work observed in our study can, at least partially, be explained by the potential healthy worker survivor effect. Except from duration of night shifts, the different categories of night work in our study were expressed by the cumulated exposure during the first 32 pregnancy weeks. Accordingly, the women with the highest exposure were those who endured night work throughout pregnancy. These women had, presumably, a relatively higher health status. As pointed out by Nabe-Nielsen and colleagues in their study surprisingly showing that shift workers had better mental health than day workers "choosing night work might be a deliberate choice based on personal needs and preferences" (44). It is however important to acknowledge that we did not have information on the reason for changing working schedules among women who stopped working night shifts after the first trimester. We can only hypothesize that these women were somehow at higher risk of developing PPD. Nevertheless, workers with depressive symptoms were found to be at risk of changing from shift to day work (relative risk 1.98, 95% CI 1.13-3.47), and from shift work to sick leave (relative risk 2.96, 95% CI 2.00-4.29) (45). Similarly, a study of changes in mental health as a predictor of changes in working time found that workers with prolonged fatigue, need for recovery or psychological distress tended to change from shift to day work (OR 3.44, 95% CI 1.42-8.38; 1.36, 0.34-5.45; and 2.26, 0.84-6.04, respectively) (46). One possible explanation for the association between depression and changes of working schedules is that worsening of depressive symptoms in relation to night work may be more easily recognizable than other disorders, such as hormonal dysfunction.

Our findings highlight the importance of identifying women who work at night that might be at risk of developing PPD, especially those who do not adapt to night work. As pregnant workers are not generally restrained from night work in Denmark, the identification of potential negative health effects of night work during pregnancy is based on individual clinical evaluation usually by a general practitioner, an obstetrician or an occupational physician. It has been shown that women with predisposition for depression may be more susceptible to hormonal and pro-inflammatory changes during pregnancy and postpartum period (17, 18, 20, 21). It is therefore possible that these women might also be more susceptible to hormonal changes and sleep disorders (22, 23, 25) induced by night work.

It is possible that the gradient of higher exposures corresponding to higher health status is also present within night work. In our study, this hypothesis is supported by findings of an increased risk of PPD among night workers without quick returns after a night shift (table 5). Quick returns are frequently not part of planned schedules (47-49), but they occur in periods of increased workload at the workplace. In this

scenario, workers with poorer health status might not to take extra shifts, avoiding quick return. Also, analysis restricted to nurses, who represent a more homogeneous group regarding organization of night shifts, workload and job tasks, suggested elevated risks of PPD in the lowest categories of exposure to night work.

Further investigation of the healthy worker survivor effect among night workers requires specific epidemiological and statistical methods (14, 50-53). For that purpose, assessment of pregnancy period-specific exposure is also necessary as changes of working schedules occur generally during the end of the first trimester, when many women, at least in Denmark, inform their workplace about their pregnancy.

Strengths and Limitations

Nationwide sample size, prospective design, detailed and register-based exposure and outcome assessment, and within-night work comparisons are the primary strengths of our study.

Even though our cohort is nationwide, our results are based on relatively few cases as only the most severe cases of PPD are treated in hospitals in Denmark. As shown by Munk-Olsen and colleagues for each birth resulting in inpatient psychiatric treatment of postpartum disorder in Denmark, 2.5 births resulted in outpatient treatment and 12 births resulted in general practitioner-provided pharmacological treatment (33). Therefore, even though the prevalence of severe PPD in our cohort (0.3%) corresponds to prior Danish population-based studies (33), low power is a limitation of our study. Misclassification of the mild cases of PPD might be an important source of bias towards the null in our cohort. The extent of this bias depends on whether night work is a risk factor specifically for mild cases of PPD. This is yet to be elucidated. Nevertheless, including only severe cases of PPD increased the specificity of the outcome.

We lacked information on how well the participants adapted to night work. Psychological resilience (hardiness) and coping seem to be strongly related to psychological well-being (54). Further, we lacked information on chronotype. This might have biased the results towards the null as the evening chronotype, which is normally more frequent among night workers than day workers, has been independently associated with the risk and severity of depression (55).

CONCLUSION

Overall, our results do not suggest that night work during pregnancy is a risk factor for severe PPD. However, we observed a 2-fold increased risk of PPD among women who stopped working night shifts after the first pregnancy trimester. This may reflect the influence of the healthy worker survivor effect, but the interpretation of this finding requires caution and warrants further attention.

Future research should use pregnancy period-specific exposure assessment and apply epidemiological and statistical methods that account for the healthy worker survivor effect.

AUTHOR CONTRIBUTIONS

Paula E. C. Hammer, Jens P. Bonde, Anne H. Garde, Esben M. Flachs, Ann D. Larsen and Ida Hageman provided substantial contributions to the conception of the study and the analysis of the data. Paula E. C. Hammer was responsible for drafting the paper. All authors contributed substantially to the interpretation of the data, the critical revision of the paper for important intellectual content.

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