

BØR GRAVIDE ARBEJDE OM NATTEN?

Et registerbaseret studie af den gravides helbred og sygefravær i forhold til natarbejde



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1. Forord

Dette projekt blev finansieret af Arbejds miljøforskningsfonden (projekt nummer 31-2015-03 2015001705), og gennemført som et Ph.d.-projekt af læge Paula Edeusa Cristina Hammer indskrevet på Københavns Universitet (KU) fra 1. januar 2016 til 31. december 2018 ved Arbejds- og Miljømedicinsk Afdeling (AMED), Bispebjerg / Frederiksberg Hospital (BBH). Ph.d.-projektet blev vejledt af professor Jens Peter Bonde (AMED, BBH/FH og KU), professor Anne Helene Garde (Det Nationale Forskningscenter for Arbejds miljø [NFA]), post.doc. Ina Olmer Specht (Parker Institut, BBH/FH), post.doc. Sesilje Bondo Petersen (AMED, BBH/FH) og professor Anja Bisgaard Pinborg (Fertilitetsklinikken, Rigshospitalet). Som led i projektet tilbragte Paula 3-måneders forskningsophold på NFA fra oktober til december 2017.

Projektet er godkendt af Datatilsynet (journal nr. BFH-2015-079, I—suite nr. 04228), og er baseret på oplysningerne fra følgende registre: 1) *Den Danske Arbejdstids Database (DAD)*, 2) *Det Medicinske Fødselsregister (MFR)*, 3) *Landspatientregisteret (LPR)*, og 4) *Det Psykiatriske Centralregister*. Etableringen af DAD blev finansieret af Arbejds miljøforskningsfonden (projekt nr. 23-2012-09), NordForsk (projekt nr. 74809) og NFA. Danske Regioner har udført og delvist finansieret overførsel af data til DAD. Jens Worm Begtrup, Lisbeth Nielsen, Anders Ørberg og Ann Dyreborg Larsen har været behjælpelige med datahåndtering af DAD. Danmarks Statistik har sørget for adækvat anonymisering af data, sammenkobling af registre samt den digitale platform for udførelsen af dataanalyse. Forskerne har derfor ikke haft adgang til personidentificerbare data.

En særlig tak rettes til følgegruppen, som har bidraget som sparringspartnere i forskningsprocessen, bestående af Jeanette Wilén Staffeldt og Sarah Walter (FOA), Helle Brieghel Bavnghøj (Dansk Sygeplejeråd), Anne-Mette Schroll og Mette Busk (Jordemoderforeningen), John Villadsen (3F, industrigruppen), Trine Lykke Loughran (Dansk Erhverv), Malene Vestergaard Sørensen (Danske Regioner), og Tina Frisk Kjettrup (Lægeforeningen – Yngre Læger).

Forfatterne, april 2019

2. English Summary

Approximately 10-14% 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. Most 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, study I), sick leave (study II), and severe postpartum depression (PPD, study III); 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 (quick returns).

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 three consecutive night shifts during the first 20 pregnancy weeks were associated with 41% increased risk of HDP, and an indication of increasing risk of HDP with increasing number of quick returns after night shifts (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 calling in sick 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 HDP among women who worked up to one night shift per week on average during pregnancy, as far as they did not have more than three 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 should be taken into account by health care professionals who advise workers and employers on health risks of night work during pregnancy.

3. Dansk resumé

Det anslås, at 10-14% af kvinderne på arbejdsmarkedet i henholdsvis Danmark 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 moderen 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 (studie I), sygefravær (studie II) og svær fødselsdepression (studie III); og 2) at identificere mulige måder at tilrettelægge natarbejde i løbet af graviditeten, 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 (*quick returns*).

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

Vi fandt, at mere end tre nattevagter i træk i løbet af de første 20 graviditetsuger øgede risikoen for hypertension og svangerskabsforgiftning med 41% (svarende til 1,4 ekstra cases blandt 100 gravide som arbejdede mere end tre nattevagter i træk i de første 20 graviditetsuger) samt en indikation på stigende risiko ved stigende antal *quick returns* efter nattevagter (studie I). Hvis den gravide kvinde var svært overvægtig, var denne risiko 4-5 gange større ved alle aspekter af natarbejdet (svarende til 3-4 ekstra cases blandt 100 svært overvægtige gravide som arbejdede om natten). I studie II fandt vi, at nattevagter, især vagter længere end 12 timer, samt med kort vagtinterval øgede risikoen for sygemelding i det efterfølgende døgn med 55% i alle graviditets-trimestre sammenlignet med dagvagter (svarende til 1,5 ekstra sygedage per 100 lange nattevagter). På den anden side fandt vi ikke nogen øget risiko for hypertension eller svangerskabsforgiftning 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 der er en risiko blandt disse kvinder, forventes den at være beskednen. I studie III fandt vi ingen øget risiko af svær fødselsdepression i forhold til natarbejde givet den mobilitet ud af natarbejde som forekommer blandt hospitalsansatte. Derimod havde kvinder, som stoppede med at arbejde om natten efter 1. graviditets-trimester, en fordobling af risikoen 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 kvinder med lavere risiko 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.

Resultaterne 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.

4. Introduktion

Tilstrækkelig hvile og søvn i takt med naturens lys/mørk cyklus bidrager til den optimale funktion af samtlige systemer i den menneskelige krop. Dette samspil er styret af flere komplekse processer allerede fra det intrauterine liv, som resulterer i kroppens døgnrytme. Forstyrrelsen af døgnrytmen medfører ændringer i denne styringsproces, og kan medføre sygdomme. Natarbejde er én af de faktorer, som kan forstyrre døgnrytmen. **PREGNIGHT**-projektet har fokuseret på helbredseffekter af natarbejde i løbet af graviditeten. Dette emne er relevant både for gravide, deres arbejdsgivere, sundhedsfaglige personer og beslutningstagere indenfor folkesundheden af mindst tre grunde:

- 1) Natarbejde er almindeligt blandt kvinder i den reproduktive alder. Der anslås at 14% af kvinderne på arbejdsmarkedet i Europa arbejder mindst én nattevagt om måneden (1).
- 2) Hvis natarbejde i løbet af graviditeten er en risikofaktor for negative helbredsudfald, kan det udover at påvirke den gravide kvinde og hendes barn i perioden efter fødslen, også påvirke hendes familieliv på langt sigt. På den måde kan natarbejde have konsekvenser for folkesundheden generelt.
- 3) Negative helbredsudfald i løbet af graviditeten kan medføre betydelig socioøkonomiske omkostninger, da disse kvinder kan have svært ved at komme tilbage på arbejde, eller ved at opretholde deres tilknytning til arbejdsmarkedet.

5. Baggrund

Døgnrytme

Den menneskelige døgnrytme er styret af kroppens 'master clock', et center i hjernen som, i respons til lys, kommunikerer til resten af kroppen om det er dag eller nat (2, 3). Denne kommunikation foregår både via nervesystemet og via en række hormoner (4). Udover lys, kan døgnrytmen blive påvirket af søvn, fysisk aktivitet, spisevaner og kroppens temperatur (5).

Reproduktion er også styret af døgnrytmen. Dette gælder fra produktionen af hormoner i hjernen eller i kønsorganerne til udvikling af en normal graviditet (6-9).

Figur 1 – Døgnrytme er med til at regulere den humane reproduktion fra dannelse af kønshormoner til befrugtning og udvikling af graviditeten.



Et af de mest undersøgte døgnrytmehormoner er melatonin, det såkaldte 'mørke hormon', der dannes om natten i koglekirtlen i hjernen (10). Det produceres også i andre organer, som knogler, leveren, huden, æggestokkene og moderkagen (11). Produktionen af melatonin stiger i løbet af graviditeten, med højeste niveauer nær termin (12). Melatonin er en af de mest effektive antioxidanter, der er med til at bekæmpe oxidative stress og inflammation (13). Derudover, bidrager det til reguleringen af immunsystemet, og i løbet af graviditeten styrer det fosterets døgnrytme og bidrager til den føtale neurologiske udvikling (14). Melatonin bidrager også til den normale funktion af moderkagen i løbet af graviditeten og til igangsættelse af fødslen (15, 16). Det er dog vigtigt at understrege, at der er mange andre hormoner og også gener (clock genes), som bidrager til reguleringen af døgnrytmen i graviditeten (17, 18). Dog er mange af disse komplekse systemer ikke fuldstændigt afklaret endnu.

Natarbejde kan forstyrre døgnrytmen ved at påvirke både hormoner, inklusiv melatonin, søvnen, og adfærd om natten såsom udsættelse for lys, fysisk aktivitet og kostindtag (19).

Døgnrytmen har også stor betydning for kontrol af blodtrykket blandt mænd, gravide og ikke-gravide kvinder (20, 21). Både søvnforstyrrelse og ændringer i melatonin produktion har vist at være risikofaktorer for forhøjet blodtryk under graviditeten og svangerskabsforgiftning (22, 23). Der er endvidere evidens for, at produktion af melatonin af moderkagen er påvirket hos kvinder, som udvikler svangerskabsforgiftning (14, 24, 25). Derudover øger de u hensigtsmæssige adfærdsmønstre som forbindes med natarbejde (nedsat fysisk aktivitet og dårlig kost) også risikoen for hjerte-kar-sygdomme generelt (26-32).

Igennem de sidste 20 år har man gradvist afklaret det komplekse samspil mellem døgnrytme og neuropsykologisk regulering. For eksempel er niveauet af neurotransmitteren serotonin (en af byggestenene til dannelsen af melatonin) lavt hos mennesker som har depression, og melatonin er indblandet i den genetiske regulering af serotonin produktion (33). Lavt melatonin-niveau i blodet er også fundet blandt gravide som har depression (34). Derudover er søvnforstyrrelser tæt forbundet med depression både blandt mænd, gravide og ikke-gravide kvinder (35, 36).

Tidligere studier

Resultater fra tidligere studier af natarbejde som risikofaktor for forhøjet blodtryk og svangerskabsforgiftning, sygefravær og fødselsdepression har været inkonsistente (se tabel 1). Evidensen om association har derfor ikke været entydig. En mulig forklaring på disse inkonsistente resultater på tværs af studier kan være deres begrænsninger i forhold til eksponeringsvurderingen. Samtlige studier anvendte selv-rapporteret og groft defineret natarbejde. De har derfor ikke haft mulighed for at undersøge hyppigheden og varigheden af natarbejde eller effekten af natarbejde på forskellige tidspunkter af graviditeten. Disse studier har heller ikke sammenlignet natarbejderne imellem. Dette er vigtigt fordi sådanne sammenligninger udføres på en mere homogen gruppe arbejdere end ved at sammenligne natarbejdere med dagarbejdere. Derudover har helbredsudfald også været selv-rapporteret i en del studier, hvilket øger risiko for informationsbias og misklassifikation af deltagerne.

Table 1 – Tidligere studier af natarbejde som risikofaktor for forhøjet blodtryk og svangerskabsforgiftning, sygefravær og depression.

Studie design (antal deltagere)	Eksponering	Helbredsudfald	Resultater (95% konfidensinterval) RR = relativ risiko OR = odds ratio HR = hazard ratio
Forhøjet blodtryk og svangerskabsforgiftning			
Case-kontrol (37) (n=368)	2- eller 3-vagtskift	Forhøjet blodtryk	RR 1,2 (0,7-2,0)
Tværsnit (38) (n=3.321)	Skiftende arbejdstid	Svangerskabsforgiftning	OR 2,0 (1,1-3,6)
Case-kontrol (39) (n=4.582)	≥ 1 time natarbejde om ugen	Forhøjet blodtryk og svangerskabsforgiftning	OR 1,0 (0,5-2,0)
Tværsnit (40) (n=24.200)	Skiftende arbejdstid	Forhøjet blodtryk; Svangerskabsforgiftning	OR 0,8 (0,4-1,4) OR 0,7 (0,3-1,8)
Kohorte (41) (n=4.465)	Nattevagter en gang imellem eller ofte	Forhøjet blodtryk; Svangerskabsforgiftning	OR 0,6 (0,3-1,4) OR 0,9 (0,3-2,8)
Sygefravær i løbet af graviditeten			
Tværsnit (42) (n=773)	Natarbejde eller skiftende arbejdstid	Sygefravær > 10% af den planlagte arbejdstid	OR 1,4 (1,0-1,9)
Kohorte (43) (n=51.875)	Skiftende arbejdstid inklusive nattevagter; > 8 nattevagter om måneden	Sygefravær > 15 dage	HR 1,6 (1,4-1,8) HR 1,9 (1,7-2,2)
Tværsnit (44) (n=1.495)	≥ 1 nattevagt i løbet af graviditeten	Sygefravær uanset varighed	Højere frekvens (ingen estimat angivet)
Kohorte (45) (n=508)	Aften- og/eller nattevagter	Sygefravær > 20 dage	OR 1,3 (0,8-2,2)
Depression blandt mænd og kvinder – ingen studie om fødselsdepression specifikt			
Meta-analyse af 5 kohorte studier (46)	Natarbejde eller skiftende arbejdstid	Depressive symptomer Forbrug af antidepressive medicin Sygefravær på grund af psykiske sygdomme	RR 1,4 (0,9-2,2)
Systematisk review af 8 tværsnit og 3 kohorte studier (47)	Skiftende arbejdstid inklusive nattevagter	Depressive symptomer	RR 1,4 (1,2-1,6)
Kohorte (48) (n=8.643)	Skiftende arbejdstid med eller uden nattevagter	Forbrug af antidepressive medicin	OR kvinder 1,0 (1,1-3,8) OR mænd 0,9 (0,5-1,6)

6. Projektets formål

Det overordnede formål af **PREGNIGHT**-projektet var at undersøge negative helbredseffekter af forskellige aspekter af natarbejde i løbet af graviditeten, samt at identificere mulige måder at tilrettelægge natarbejde på som kan mindske eventuelle helbredsrisici. Mere specifikt undersøgte vi:

- **Studie I** - Risiko for forhøjet blodtryk og svangerskabsforgiftning i forhold til antal og varighed af nattevagter, nattevagter i træk og tid mellem vagterne i løbet af de første 20 graviditetsuger ved sammenligninger både af natarbejdere versus dagarbejdere og natarbejderne imellem;
- **Studie II** - Risiko for sygemelding startende på samme eller dagen efter nattevagter versus dagvagter med kvinder som deres egne kontrol; og
- **Studie III** - Risiko for svær fødselsdepression i forhold til antal og varighed af nattevagter, nattevagter i træk og tid mellem vagterne i løbet af de første 32 graviditetsuger ved sammenligninger både af natarbejdere versus dagarbejdere og natarbejderne imellem.

7. Fremgangsmåde

Registre

Vi udførte et landsdækkende kohortestudie baseret på fire danske registre:

1. Kildepopulationen til studierne blev identificeret fra den *Danske Arbejdstids Database (DAD)*, som indeholder arbejdstidsregistrering på alle regionsansatte i Danmark, mere end 250.000 ansatte, som inkluderer alle ansatte på offentlige hospitaler (49). Registeret er det største af sin slags i verden. Det angiver start og slut tidspunkt for samtlige arbejdsdage og fravær, job titel og ansættelsessted fra januar 2007 til december 2015. Validiteten af data fra DAD anses for at være høj, fordi det bruges til lønberegninger. Dog kan varigheden af vagterne og af ugentlige arbejdstimer være underestimeret blandt ansatte for hvem ubetalte overarbejde er hyppigt, for eksempel blandt læger.
2. *Det Medicinske Fødselsregister (MFR)*, som indeholder oplysninger om alle fødsler i Danmark, både på hospitaler og hjemmefødsler, siden 1973 (50). Vi anvendte data om kvindens alder, *body mass index (BMI)*, paritet, rygning og gestationsalder i dage, samt barnets fødselsdato. Validiteten af data fra MFR er høj, og nogle af oplysninger trækkes direkte fra CPR-registeret.
3. Ved hjælp af *Landspatientregisteret (LPR)*, som indeholder oplysninger om indlæggelser siden 1977 og af ambulante kontakter siden 1994 (51), identificerede vi tilfælde af forhøjet blodtryk og svangerskabsforgiftning til studie I, og af fødselsdepression til studie III. Data fra LPR har vist sig at være af høj validitet og fyldestgørende for alvorlige sygdomme generelt (52).
4. Ved hjælp af det *Psykiatriske Centralregister*, som indeholder oplysninger om psykiatriske indlæggelser siden 1969 og af ambulante kontakter siden 1995 (53), identificerede vi tilfælde af fødselsdepression til studie III. Dette register har også høj validitet for alvorlige diagnoser generelt.

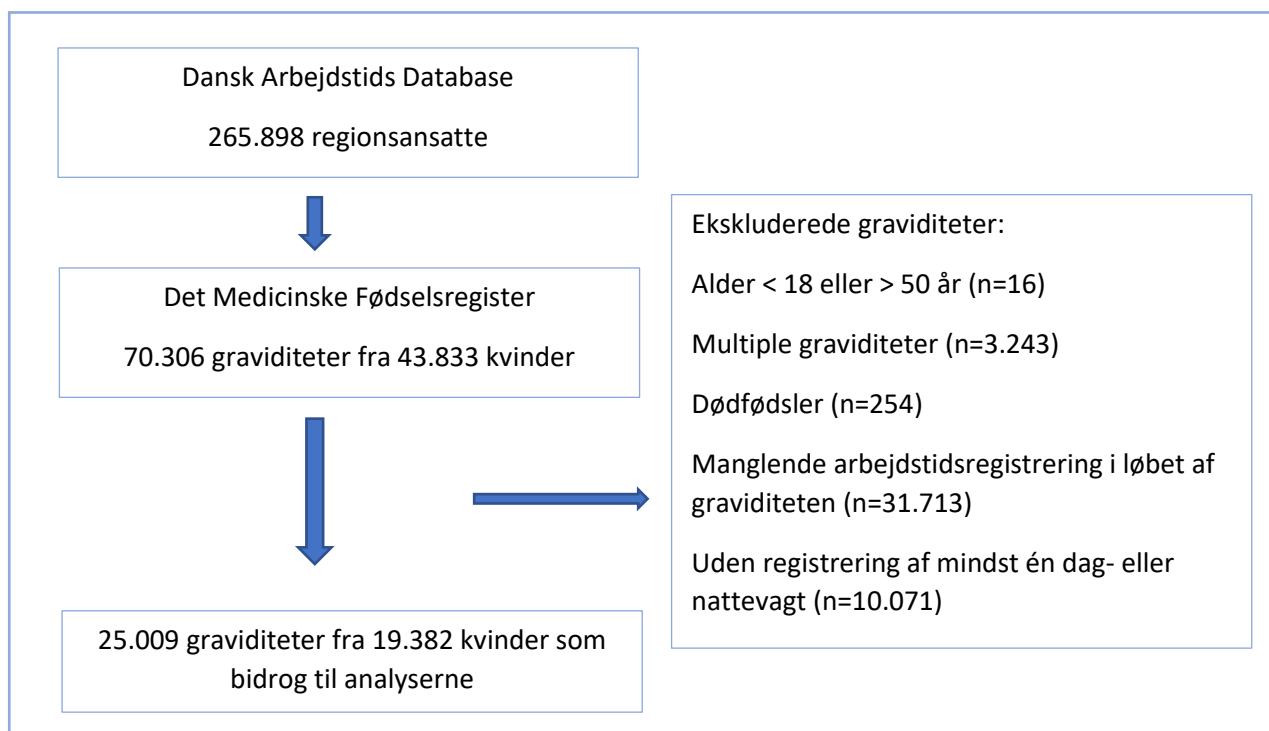
Studiekohorten

Kvinder fra DAD, som fødte (det vil sige som optrådte i MFR) mindst én gang i perioden 2007-2013, dannede studiekohorten for studie I og II (42.485 kvinder), og i perioden 2007-2015 for studie III (43.833 kvinder). Vi ekskluderede kvinder yngre end 18 eller ældre end 50 år gammel, multiple graviditeter (for eksempel tvillinger), graviditeter som manglede arbejdstidsregistrering eller uden registrering af mindst én dag- eller nattevagt (for eksempel graviditeter kun med aftenvagter). Den endelige studiekohorte inkluderede 18.724 kvinder med enten fast dagarbejde eller mindst én nattevagt i de første 20 graviditetsuger til studie I, og 19.382 kvinder med enten fast dagarbejde eller mindst én nattevagt i de første 32 graviditetsuger til studie III.

I studie II anvendte vi kvinderne som deres egen kontrol for at undersøge risiko for sygemelding startende på samme eller dagen efter nattevagter versus dagvagter. Derfor inkluderede vi kun kvinder som havde mindst én dagvagt og én nattevagt og én sygefraværsdag i de første 32 graviditetsuger. Det resulterede i 9.799 kvinder som studiekohorte for analyser om sygefravær.

Klassifikation af socioøkonomisk status (SES) som høj, mellem eller lav var baseret på Danmarks Statistiks klassifikation med udgangspunkt i DISCO-koder (54, 55).

Figur 2 – Dannelse af studiekohorten i periode 2007-2015.



Eksponeringsvurdering

Type, antal og varighed af samtlige vagter og fravær blev fordelt per graviditetsuge fra konceptions- til fødselsdato. Konceptionsdatoen blev estimeret ved at trække gestationsalderen i dage fra fødselsdatoen.

Vagter varende mindst tre timer blev defineret som

- **Dagvagt** = start efter kl 06.00 og slut før kl 21.00,
- **Morgenvagt** = start efter kl 03.00 og før kl 06.00,
- **Aftenvagt** = slut efter kl 21.00 og før kl 02.00, og
- **Nattevagt** = arbejde mellem kl 23.00 og kl 06.00 uanset start eller slut tidspunkt.

Baseret på tidligere studier med lignende eksponeringsdata og lignende kohorte (56, 57) definerede vi følgende aspekter af natarbejde som relevante eksponeringer:

- **Antal nattevagter.** Det samlede antal nattevagt var 1-19 eller ≥ 20 (svarende til cirka én nattevagt om ugen i de første 20 graviditetsuger) i studie I, og 1-8 eller ≥ 9 (svarende til cirka én nattevagt om måneden) i studie II.
- **Varighed af nattevagter** blev defineret som ≤ 8 timer, $> 8-12$ timer eller > 12 timer (lange nattevagter).
- **Nattevagter i træk** blev vurderet som enkelte nattevagter, 2-3 nattevagter i træk eller > 3 nattevagter i træk.
- **Tid mellem vagterne**, det vil sige tiden mellem to vagter i træk, blev defineret som < 11 timer (*quick returns*) uanset vagttypen eller < 28 timer efter nattevagter (*quick returns* efter nattevagter).

Natarbejdere blev defineret som kvinder med mindst én nattevagt i løbet af eksponeringstiden, men dagarbejdere var kvinder med mindst én dagvagt uden morgen-, aften- eller nattevagt.

Helbredsudfald

Diagnose-koder fra LPR eller det Psykiatriske Centralregister er baseret på den 8. version af den *International Classification of Diseases (ICD-8)* frem til 1993 og den 10. version (*ICD-10*) siden 1994 (58). Alle diagnoser blev defineret som tidligere, nuværende eller efter fødslen i forhold til hver graviditet.

Tilfælde af forhøjet blodtryk og svangerskabsforgiftning i studie I blev undersøgt sammen, fordi de betragtes klinisk som en samlet sygdommens enhed. De blev identificeret ved følgende diagnose-koder:

- ICD-8: 400-404 (hypertension), 636 (nyresygdom i graviditeten eller efter fødslen) og 639 (svangerskabsforgiftning) eller
- ICD-10: I10-15 (hypertension), O12, 13, 16 (gestationel hypertension), O14, 15 (svangerskabsforgiftning).

Sygefravær i studie II blev defineret ved DAD-registrering 'Syg' varende mindst tre timer.

Tilfælde af fødselsdepression i studie III blev identificeret ved følgende diagnose-koder:

- ICD-8: 296.0 (melancholia) og 300.4 (depressiv neurosis) eller
- ICD-10: F32 (depressiv episode), F33 (tilbagevendende depressiv episode).

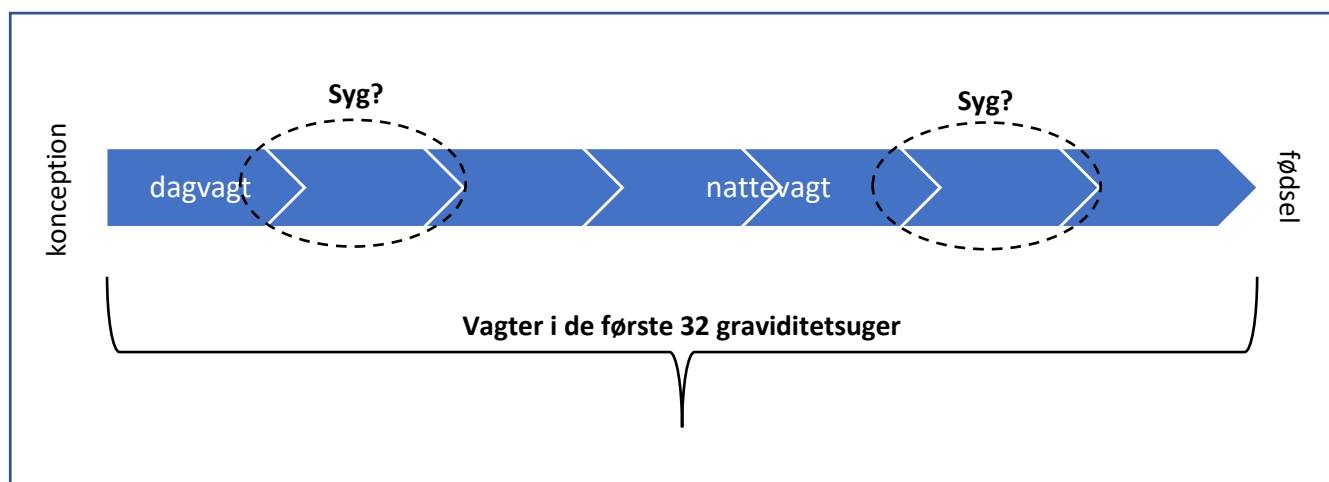
Ved at identificere tilfælde af fødselsdepression ud fra hospitalsregistre, har vi primært undersøgt risikoen for svær fødselsdepression, som kræver hospitalsbehandling enten med indlæggelse eller ambulante forløb. De fleste tilfælde af mild til moderat fødselsdepression behandles i primærsektoren af praktiserende læger eller privat praktiserende psykiatere (59).

Statistiske analyser

Studie I. Vi brugte logistisk regression til at undersøge risikoen for forhøjet blodtryk og svangerskabsforgiftning i forhold til antal og varighed af nattevagter, nattevagter i træk og tid mellem vagterne i de første 20 graviditetsuger. Eksponeringstiden var 20 uger fordi graviditetsrelateret forhøjet blodtryk og svangerskabsforgiftning først kan diagnosticeres efter den 20. graviditetsuge. På den måde sikrede vi os at natarbejde forekom før sygdommen. Hvis en kvinde har forhøjet blodtryk før dette tidspunkt, betragtes det som kronisk forhøjet blodtryk, det vil sige at kvinden højst sandsynligt havde sygdom allerede før graviditeten. Analyserne var justeret for alder, BMI, paritet, rygning, SES og sygefravær tre måneder før graviditeten. I alle analyser sammenlignede vi både natarbejdere versus dagarbejdere og natarbejderne imellem.

Studie II. Vi brugte *fixed effects* logistisk regression (60) til at undersøge risikoen for sygemelding som startede på samme dag eller dagen efter nattevagter versus dagvagter med kvinder som deres egen kontrol i de første 32 graviditetsuger. Med andre ord, har vi med denne statistiske model besvarede spørgsmålet: ”*Forårsager en ændring af eksponeringen (dag- / nattevagt) en ændring af udfaldet (syg / ikke syg)?*”. Ved at undersøge forekomsten af sygemelding indenfor kort tid efter nattevagterne, undersøgte vi korttidseffekten af natarbejde som risikofaktor for sygefravær. Denne korttidseffekt skyldes højst sandsynligt træthed og søvnforstyrrelse, som ikke indhentes med blot én ’sovedag’, fremfor forekomsten af kroniske sygdomme som årsag til sygemelding. Da kvinderne var deres egne kontrol, var der ikke behov for at justere analyserne for personlige faktorer som alder, socioøkonomisk status eller paritet.

Figur 3 – Illustration af den statistiske model anvendt i studie II af PREGNIGHT-projektet til at undersøge risikoen for sygefravær som startede på samme dag eller dagen efter nattevagter versus dagvagter med kvinder som deres egne kontrol.



Studie III. Vi brugte logistisk regression til at undersøge risikoen for svær fødselsdepression i forhold til antal og varighed af nattevagter, nattevagter i træk og tid mellem vagterne i de første 32 graviditetsuger. Eksponeringstiden var 32 uger fordi de fleste kvinder i kohorten gik på barselsorlov otte uger før terminsdato. Analyserne var justeret for alder, BMI, paritet, SES, sygefravær tre måneder før graviditeten og tidligere depressionsdiagnose fra registrene. I alle analyser sammenlignede vi både natarbejdere versus dagarbejdere og natarbejderne imellem.

I alle studier udførte vi sensitivitetanalyser begrænsede til de største faggrupper i kohorten, nemlig sygeplejersker og læger, og til førstegangsfødende. I studie III har vi yderligere undersøgt, om der var forskel på forekomsten af svær fødselsdepression hos kvinder som stoppede med at arbejde om natten i løbet af 1. eller 2. trimester i forhold til kvinder som arbejdede om natten i alle trimestre. På den måde undersøgte vi om kvinder, som på en eller anden måde er mere sårbare for fødselsdepression, stopper med at have natarbejde i løbet af graviditeten, den såkaldte *healthy worker survivor* effekt (61, 62). Med andre ord, betyder denne effekt at kvinder som arbejder om natten i løbet af hele graviditeten, er sundere end dem der stopper med at arbejde om natten undervejs. Hvis det er tilfældet, vil analyserne som tager hele graviditetsperioden i betragtning resultere i en underestimering af risikoen for svær fødselsdepression i forhold til natarbejde.

Alle analyser blev udført på Danmarks Statistiks digitale platform med SAS 9.4 Software (SAS Institute, Cary, North Carolina, United States).

8. Hovedresultater

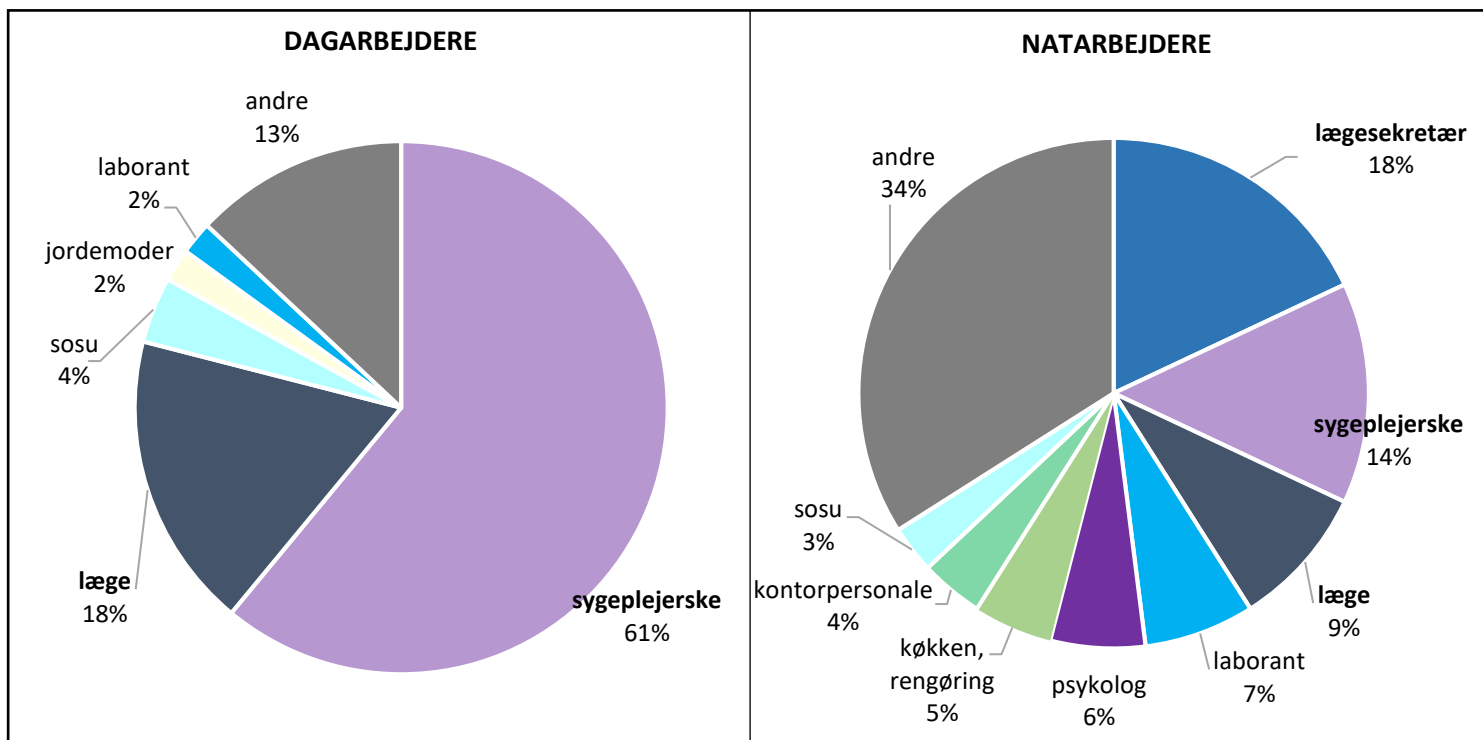
Demografiske og arbejdstidskarakteristika

Cirka 60% af studiekohorten (svarende til cirka 12.000 kvinder) var natarbejdere, det vil sige havde mindst én nattevagt i de første 32 graviditetsuger. De havde i gennemsnit to nattevagter om måneden og næsten 20% af alle deres vagter var nattevagter. De fleste natarbejdere var sygeplejersker (64%) eller læger (17%), mens de fleste dagarbejdere var lægesekretærer (18%), sygeplejersker (15%) eller fysioterapeuter (14%) – se figur 4. Begge grupper havde lignende alder (32 år i gennemsnit) og BMI (24 kg/m² i gennemsnit). Lav SES og rygning var højere blandt dagarbejderne (18% og 3% versus 6% og 2% blandt natarbejderne).

Blandt kvinder med mindst én nattevagt i de første 32 graviditetsuger var forekomsten af de forskellige aspekter ved natarbejde som vi undersøgte som følgende: 8% havde mere end én nattevagt om ugen; 39% havde mindst én nattevagt som varede > 12 timer; 18% havde > 3 nattevagter i træk; 70% havde mindst én *quick return*; og 93% mødte på arbejdet < 28 timer efter en nattevagt mindst én gang – se figur 5.

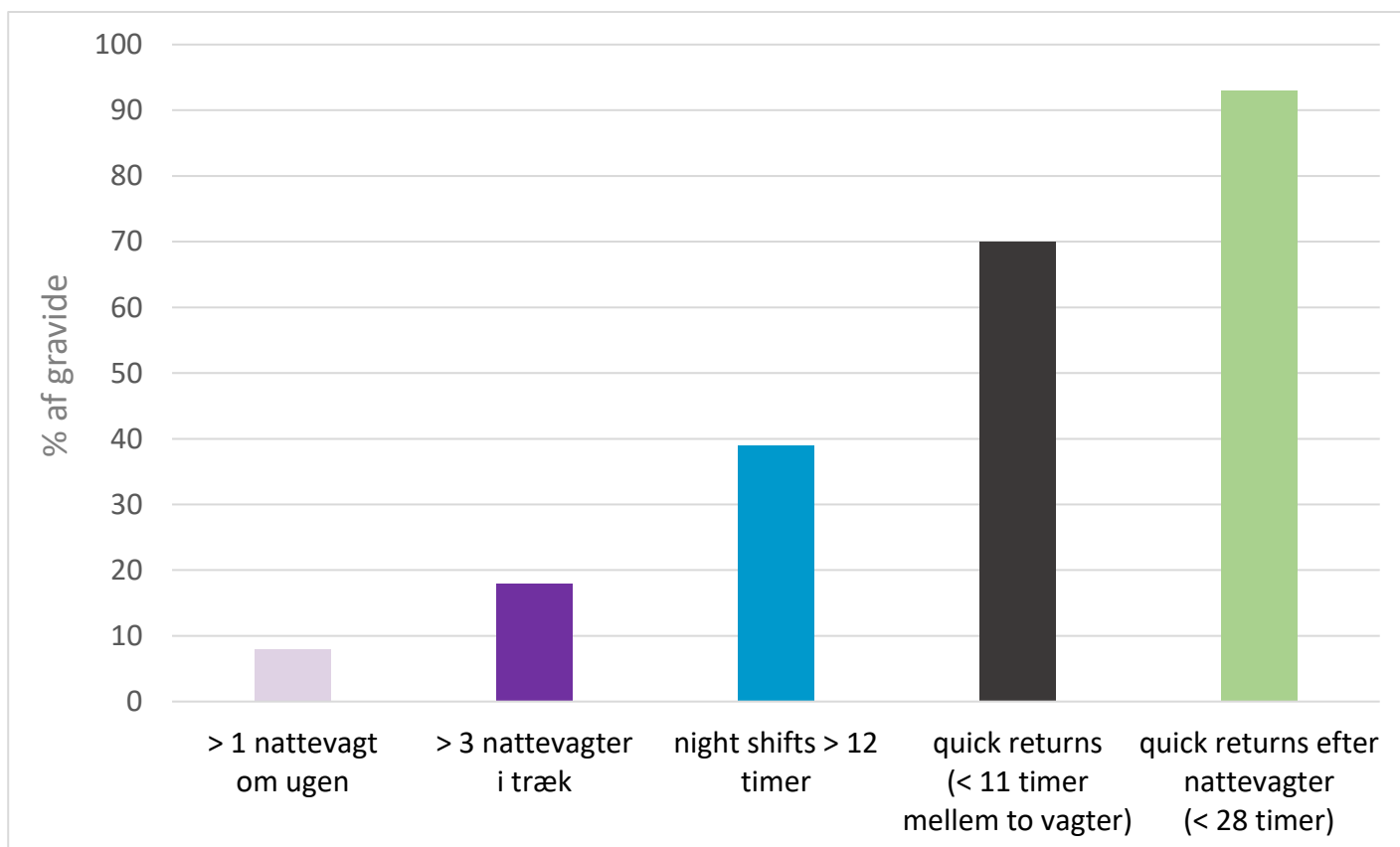
Sygeplejersker og læger havde væsentlige forskelle ved tilrettelæggelse af natarbejde. Sygeplejersker havde for eksempel flere aftenvagter, flere nattevagter ≤ 12 timer, flere nattevagter i træk og flere *quick returns*. De havde på den anden side færre ugentlige arbejdstimer sammenlignet med lægerne. Lægerne havde ikke > 3 nattevagter i træk, formentlig fordi de næsten udelukkende havde nattevagter > 12 timer. Angående deres livstilsfaktorer havde sygeplejerskerne væsentlig højere forekomst af rygning (2%) end lægerne (0,2%).

Figur 4 – Jobtitler på studiedeltagere i *PREGNIGHT*-projektet.



* sosu = social- og sundhedsassistent; dagarbejdere = udelukkende dagvagter i de første 32 graviditetsuger; natarbejdere = mindst én nattevagt i de første 32 graviditetsuger.

Figur 5 – Aspekter af natarbejde undersøgt i *PREGNIGHT*-projektet blandt cirka 12.000 gravide som arbejdede mindst én nattevagt i de første 32 graviditetsuger.



Studie I – Forhøjet blodtryk og svangerskabsforgiftning

Forekomsten af forhøjet blodtryk og svangerskabsforgiftning var lavere i vores studiekohorte (4%) end den observerede i den danske befolkning (6%) (63).

Tabel 2 viser en oversigt over hovedresultaterne fra studie I. Vi fandt ingen risiko øgning ved sammenligninger af natarbejdere versus dagarbejdere. Ved sammenligningerne natarbejderne imellem, som er en mere homogen gruppe, fandt vi at flere end 3 nattevagter i træk øgede risikoen for forhøjet blodtryk og svangerskabsforgiftning. Forekomsten af hypertension og svangerskabsforgiftning i referencegruppen (kvinder som arbejdede om natten men uden at have nattevagter i træk) var 3,3 cases per 100 gravide. Vi fandt en risiko øgning på cirka 40%, som svarer til 1,4 ekstra cases blandt 100 gravide som arbejdede > 3 nattevagter i træk i de første 20 graviditetsuger. Usikkerheden på risikoestimatet strækker sig fra 0,1 til 3,2 ekstra cases. Vi observerede endvidere en tendens til stigende risiko med stigende antal *quick* returns efter nattevagter, men selve risikoestimatet var ikke statistisk signifikant (OR 1,28; 95% konfidensinterval 0,87-1,95).

Blandt de svært overvægtige (BMI $\geq 30\text{kg/m}^2$) gravide, som i forvejen er i væsentlig forhøjet risiko for at udvikle forhøjet blodtryk og svangerskabsforgiftning, fandt vi en 4-5 fordobling af risikoen blandt natarbejderne, hvis de i løbet af de første 20 graviditetsuger arbejdede:

- én eller flere nattevagt om ugen, svarende til 2,7 ekstra cases ud af 100 svært overvægtige gravide. Usikkerheden på risikoestimatet strækker sig fra 0,2 til 10,2 ekstra cases; eller
- mindst én nattevagt varende > 12 timer, svarende til 3,6 ekstra cases ud af 100 svært overvægtige gravide. Usikkerheden på risikoestimatet strækker sig fra 0,7 til 11,0 ekstra cases; eller
- > 3 nattevagter i træk, svarende til 4,3 ekstra cases per 100 svært overvægtige gravide. Usikkerheden på risikoestimatet strækker sig fra 1,0 til 13,2 ekstra cases; eller
- ≥ 5 *quick* returns efter en nattevagt (vagtinterval af < 28 timer), svarende til 3,6 ekstra cases ud af 100 svært overvægtige gravide. Usikkerheden på risikoestimatet strækker sig fra 0,8 til 11,4 ekstra cases.

For at perspektivere de ovenstående risici, skal man bemærke, at der var i alt 1,588 svært overvægtige gravide, svarende til 9% af kohorten, i studieperioden (2007-2013). Blandt dem var der 917 gravide, som arbejdede om natten i løbet af de første 20 graviditetsuger. Derfor vil risiko ved > 3 nattevagter i træk blandt svært overvægtige gravide svare til 39,4 ekstra cases af forhøjet blodtryk eller svangerskabsforgiftning over en 7-årig periode (eller cirka 5,6 cases/år).

Vi fandt ingen risiko øgning blandt dem, der arbejdede op til 1 nattevagt om ugen i gennemsnit i de første 20 graviditetsuger såfremt de ikke havde > 3 nattevagter i træk eller var svært overvægtige. Hvis der er en øget risiko blandt dem, er den beskeden.

De tidligere fem studier, som undersøgte sammenhængen mellem hypertension og/eller svangerskabsforgiftning i forhold til natarbejde i løbet af graviditeten, viste inkonsistente resultater (37-41). Disse studier anvendte groft definerede og selvrapporterede oplysninger om arbejdstider, og alle på nær én var tværsnitstudier, hvilket vanskeliggør vurderingen af en eventuel årsagssammenhæng.

Table 2 – Hovedresultater fra **PREGNIGHT**-projekt studie I om forhøjet blodtryk og svangerskabsforgiftning.

Kohorte	Statistisk analyse	Eksponering	Resultater OR = odds ratio (95% konfidensinterval)
18.724 kvinder med fast dagarbejde eller mindst én nattevagt i de første 20 graviditetsuger	Logistisk regression justeret for alder, BMI, rygning, SES, paritet og sygefravær tre måneder før graviditeten	> 1 nattevagt om ugen Nattevagter > 12 timer > 3 nattevagter i træk ≥ 5 <i>quick returns</i> ≥ 5 <i>quick returns</i> efter nattevagter	Sammenlignet med dagarbejdere OR 1,1 (0,9-1,5) OR 1,0 (0,8-1,2) OR 1,1 (0,9-1,5) OR 0,9 (0,7-1,2) OR 1,1 (0,9-1,3) Sammenligninger natarbejderne imellem OR 1,2 (0,9-1,5) OR 1,1 (0,9-1,4) OR 1,4 (1,0-2,0) OR 1,1 (0,8-1,5) OR 1,3 (0,9-2,0) Analyser blandt svært overvægtige, sammenlignet med dagarbejdere* OR 1,2 (0,7-2,0) OR 1,2 (0,7-2,0) OR 1,2 (0,7-2,0) OR 1,2 (0,7-2,0) OR 1,2 (0,7-2,0)

* på grund af lav statistisk styrken var det ikke muligt at udføre sammenligninger natarbejderne imellem blandt svært overvægtige gravide.

Studie II – Sygefravær

Angående totalt antal af sygefraværsdage i de første 32 graviditetsuger havde 52% af kvinderne op til 14 dage, 13% havde 15-28 dage og 35% havde mere end 28 dage.

Nattevagter, især vagter længere end 12 timer, øgede risikoen for sygemelding i det efterfølgende døgn uafhængigt af personlige faktorer (dvs. kvinderne var deres egen kontrol) i alle graviditets trimestre. Forekomsten af sygefravær efter dagvagter (referencegruppen) var 2,8 per 100 dagvagter. Vi fandt en risiko øgning på 20% for alle nattevagter uanset varigheden af vagterne. Denne risiko var 40% blandt kvinder > 35 år gammel, og 55% efter nattevagter længere end 12 timer. Dette svarer til 1,5 ekstra sygedage per 100 lange nattevagter i løbet af de første 32 graviditetsuger. Usikkerheden på risikoestimatet strækker sig fra 1,2 til 1,9 ekstra cases. Lægerne havde de højeste estimater, formentlig fordi over 99% af deres nattevagter varede > 12 timer, mens andelen af lange nattevagter blandt sygeplejerskerne kun var 7%.

Vores resultater stemmer overens med fire tidligere studier, som undersøgte sammenhængen mellem natarbejde i løbet af graviditeten og risiko for sygefravær (42-45). Vores studie er dog det første som påviste en kortidseffekt af natarbejde uafhængigt af personlige faktorer.

Tabel 3 – Hovedresultater fra **PREGNIGHT**-projekt studie II om sygemelding som startede på samme dag eller dagen efter nattevagter.

Kohorte	Statistisk analyse	Eksposering	Resultater OR = odds ratio (95% konfidensinterval)
9.799 kvinder med mindst én dagvagt og én nattevagt og én sygefraværsdag i de første 32 graviditetsuger	<i>Fixed effects</i> logistisk regression*	Nattevagter versus dagvagter	1.trimester OR 1,3 (1,2-1,4) 2.trimester OR 1,3 (1,2-1,4) 3.trimester OR 1,1 (1,0-1,3)
		Nattevagter > 12 timer versus dagvagter	1.trimester OR 1,6 (1,4-1,8) 2.trimester OR 1,6 (1,4-1,9) 3.trimester OR 1,4 (1,1-1,8)

* da kvinder var deres egne kontrol, var der ikke behov for at justere analysen for personlige faktorer som alder, SES eller paritet.

Studie III – Svær fødselsdepression

Forekomsten af svær fødselsdepression i vores studiekohorte var 0,3%, hvilket svarede til tidligere danske register-studier (43, 45). Som forventet havde kvinder med fødselsdepression hyppigere en tidligere diagnose af depression (20%) i forhold til kvinder som ikke udviklede fødselsdepression (2%).

Vi fandt ingen øget risiko for svær fødselsdepression blandt kvinder, som arbejdede om natten – hverken i forhold til hyppigheden eller varigheden af nattevagterne. Dog observerede vi, at kvinder som stoppede med at arbejde om natten i løbet af 1. graviditetstrimester (n=3.094, svarende til 22% af kvinder som arbejdede om natten i 1. trimester) havde en fordobling af risiko for svær fødselsdepression sammenlignet med kvinder, som arbejdede om natten i alle trimestre (n=10.978) – se tabel 4. Dette tyder på den såkaldte *healthy worker survivor* effekt, det vil sige at kvinder, som på en eller anden måde er mere sårbar for fødselsdepression stoppede med at have natarbejde i løbet af graviditeten. Dette fund er på linje med tidligere studier, som påviste en 2 til 3-dobling af risikoen, når arbejdstiden blev ændret fra nat- til dagarbejde blandt medarbejdere med depressive symptomer eller udbrændthed (64-66). Det er dog vigtigt at understrege, at vi ikke havde oplysninger om årsagen til at kvinderne i vores studie stoppede med at arbejde om natten, og at resultatet er baseret på blot 16 tilfælde af fødselsdepression. Man skal derfor være varsom med at fortolke dette fund i vores studie.

Vi kan ikke udtale os om risiko for mild til moderat fødselsdepression, som behandles hovedsageligt i primærsektoren. Dels fordi vi ikke havde oplysninger om det, og dels fordi svær fødselsdepression baseret på tidligere studier ser ud til at involvere andre risikofaktorer end mild fødselsdepression (67).

Tabel 4 – Hovedresultater fra *PREGNIGHT*-projekt studie III om svær fødselsdepression.

Kohorte	Statistisk analyse	Eksponering	Resultater OR = odds ratio (95% konfidensinterval)
19.382 kvinder med fast dagarbejde eller mindst én nattevagt i de første 32 graviditetsuger	Logistisk regression justeret for alder, BMI, SES, paritet, sygefravær tre måneder før graviditeten og tidligere diagnose af depression	<p>> 1 nattevagt om ugen</p> <p>Nattevagter > 12 timer</p> <p>> 3 nattevagter i træk</p> <p>≥ 5 <i>quick returns</i></p> <p>≥ 5 <i>quick returns</i> efter nattevagter</p>	<p>Sammenlignet med dagarbejdere</p> <p>OR 0,6 (0,3-1,1)</p> <p>OR 0,7 (0,4-1,4)</p> <p>OR 0,6 (0,2-1,3)</p> <p>OR 0,8 (0,3-2,2)</p> <p>OR 0,6 (0,3-1,2)</p> <p>Sammenligninger natarbejderne imellem</p> <p>OR 0,7 (0,4-1,2)</p> <p>OR 0,8 (0,3-2,0)</p> <p>OR 0,7 (0,2-2,1)</p> <p>OR 0,8 (0,2-2,4)</p> <p>OR 0,3 (0,1-0,7)</p> <p>Kvinder som stoppede med arbejde om natten i</p> <p>1. trimester OR 2,1 (1,1-4,0)</p> <p>2. trimester OR 0,8 (0,4-1,8)</p> <p>sammenlignet med kvinder som arbejdede om natten i alle trimestre</p>

9. Diskussion

Fordele og ulemper ved sammenligninger med dagarbejdere og natarbejderne imellem

De sædvanlige sammenligninger mellem dag- og natarbejdere afslører den totale effekt af samtlige faktorer som adskiller disse grupper, og ikke nødvendigvis den isolerede effekt af natarbejde. Fra et epidemiologisk synspunkt er det en stor udfordring at kunne tage højde for forskelle i arbejdsindholdet og personlige faktorer relaterede til dag- og natarbejde. Et eksempel på det er selektion af sårbare personer ud af natarbejde, som resulterer i en gruppe af forholdsvis sunde personer som fortsat arbejder om natten igennem længere perioder. Dette kan skjule de eventuelle negative helbredseffekter af natarbejde (den såkaldte *healthy worker survivor* effekt), som påviste af tidligere studier (64-66). Denne effekt udgør et mindre problem i sammenligninger natarbejderne imellem. På den anden side mangler disse sammenligninger en ikke-eksponeret gruppe. Det er derfor anbefalelsesværdigt at have begge typer sammenligninger i ethvert studie af helbredseffekter af natarbejde.

De forskellige aspekter af natarbejde er tæt forbundet

Af forskningsmæssige årsager forsøger man at adskille effekten af de forskellige aspekter ved natarbejde. Men disse aspekter er i realiteten tæt forbundet. For eksempel havde lægerne i vores kohorte stort set udelukkende lange nattevagter, men ikke særlig mange nattevagter i træk. Sygeplejerskerne derimod havde fortrinsvist korte nattevagter, men flere nattevagter i træk og flere *quick returns*. Alligevel ser det ud til at antal nattevagter om ugen, antal nattevagter i træk og varighed er nattevagter er nogle af de væsentligste risikofaktorer for negative helbredsudfald i graviditeten. Udover øget risiko for sygefravær, forhøjet blodtryk og svangerskabsforgiftning, har vi i et studie finansieret af en anden bevilling, fundet at mere end én nattevagt om ugen i de første 22 graviditetsuger øger risikoen for ufrivillig abort med 30% (68).

Selvom vi ikke havde oplysninger om arbejdsindholdet på de forskellige vagter, fandt vi indikationer på at kombination af lange nattevagter med øget travlhed kan være årsagen til øget sygemelding efter lange nattevagter. For eksempel da sygeplejerskerne primært havde nattevagter af 8 timer, skyldtes forekomsten af længere nattevagter blandt dem, at de arbejdede flere vagter i forlængelsen af hinanden. Dette er som regel nødvendigt på en hospitalsafdeling, når der opstår overbelægning af patienter eller utilstrækkelig bemanding blandt personalet. Angående læger, selv om de har mulighed for sovepause eller rådhedsvagt om natten i højere grad end sygeplejerskerne, er det almindeligt at disse muligheder ikke kan udnyttes i perioder med øget travlhed.

Vores fund af øget risiko for sygefravær, forhøjet blodtryk og svangerskabsforgiftning i forbindelse med *quick returns* efter nattevagter og konsekutive nattevagter støtter tidligere studier, som påviste behov for mindst to fridage efter nattevagter for at justere søvnen tilbage til dagrytme (69-72). Derudover bidrager natarbejde under alle omstændigheder til forværring af søvnforstyrrelsen og trætheden, som er fysiologisk forbundet med graviditeten (73).

Forværende faktorer

Alder over 35 år og svær overvægt er velkendte risikofaktorer for graviditetskomplikationer (74-76). Det at vi fandt betydelig højere risiko for henholdsvis sygefravær, forhøjet blodtryk og svangerskabsforgiftning blandt disse kvinder støtter en mulig kausal sammenhæng mellem natarbejde og øget risiko for graviditetskomplikationer.

Metodologiske overvejelser

De væsentligste metodologiske styrker ved vores studier er:

- Anvendelse af landsdækkende registre som resulterede i at størrelsen på studiepopulation bidrog til den statistiske styrke af analyserne.
- Anvendelse af detaljerede daglige oplysninger om arbejdstid, som muliggjorde analysen af forskellige aspekter af natarbejde på forskellige tidspunkter af graviditeten.
- Prospektivt design, det vil sige at natarbejde skete før debut af sygdom.
- Anvendelse af lægelig stillede fremfor selv-rapporterede diagnoser.

Alligevel har studierne haft nogle væsentlige begrænsninger. For det første havde vi ikke oplysninger om arbejdsindholdet, det vil sige om hvilke arbejdsopgaver kvinderne udførte under vagterne. Dette er vigtigt, fordi effekten af natarbejdet kan variere i kombination med andre arbejdseksponeringer som fysisk krævende arbejde og psykosociale faktorer. For det andet havde vi heller ikke oplysninger om individuel tilpasning til natarbejde. Dette indebærer kronotype, altså om man er A- eller B-menneske, og mulighed samt personlige præferencer for at vælge dag- eller natarbejde.

Angående generaliserbarhed gælder vores resultater primært for kvinder med lignende arbejdstider og indenfor lignende brancher som dem i vores studiekohorte. Dette er især vigtigt, fordi de viste sig at være relative sundere end den generelle danske befolkning. For eksempel havde de væsentlig lavere forekomst af rygning og overvægt (henholdsvis 3% og 12% versus 19% og 46%) (77, 78). Dette afspejler højst sandsynligt, at kvinderne i vores kohorte er sundhedsfaglige personer. Det er derfor muligt at helbredseffekterne af natarbejde i løbet af graviditeten er endnu mere prominente blandt kvinder med en anden profil af personlige risikofaktorer, eller som har andre arbejdsmæssige eksponeringer som tungt fysisk arbejde og støj i kombination med natarbejde.

10. Konklusion

Vi fandt at natarbejde i løbet af graviditeten, især lange nattevagter og nattevagter i træk, øgede risikoen for sygefravær samt forhøjet blodtryk og svangerskabsforgiftning med henholdsvis 50% og 40%. Svært overvægtige gravide, som i forvejen er i øget risiko for en række komplikationer, havde en 4 til 5-fordobling af risikoen for forhøjet blodtryk og svangerskabsforgiftning. Vi fandt ingen øget risiko af svær fødselsdepression i forhold til natarbejde givet den mobilitet ud af natarbejde som forekommer blandt hospitalsansatte. Disse resultater var konsistente på tværs af studier, som anvendte forskellige statistiske modeller.

Vores resultater støtter hypotesen om, at de negative helbredseffekter af natarbejde i løbet af graviditeten ikke blot er et spørgsmål om ja eller nej til nattevagter, men mest om hvordan de tilrettelægges. Dette bekræftes af at vi ikke fandt en øget risiko for de ovennævnte helbredsudfald blandt kvinder, som arbejdede op til én nattevagt om ugen i gennemsnit, såfremt de ikke havde over tre nattevagter i træk eller var svært overvægtige. Hvis risikoen findes blandt disse kvinder, forventes den at være beskeden.

11. Fremadrettede perspektiver

I Danmark bliver gravide ikke konsekvent afholdt fra at arbejde om natten. Identifikation af mulige negative helbredseffekter af natarbejde hviler på individuel vurdering, som regel udført af egen læge eller en specialist i arbejdsmedicin.

Disse resultater giver anledning til overvejelser af, 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.

I lyset af, at en væsentlig del af arbejdsmarkedet repræsenteres af kvinder, som arbejder om natten, ville fravær af disse kvinder medføre væsentlige socioøkonomiske konsekvenser. På den anden side bør alle risikofaktorer for de gravides helbred som kan modificeres, tages i betragtning af sundhedsfaglige personer som rådgiver gravide og arbejdspladser, samt af beslutningstagere indenfor folkesundheden.

På trods af en række metodologiske styrke i vores studier, bør vores resultater reproduceres af andre forskningsgrupper. Vi anbefaler anvendelse af tydelige definitioner og flere aspekter af natarbejde på forskellige tidspunkter i løbet af graviditeten i fremtidig forskning. Mulige fremadrettede forskningsmæssige overvejelser kan inkludere:

- Interventionsstudier med fokus på specifikke aspekter af natarbejde i graviditeten, hvilket ville være den ultimative bekræftelse af en årsagssammenhæng;
- Studier som kombinerer arbejdstidsregistrerings data med faktorer forbundet med individuel tilpasning til natarbejde, såsom kronotype og psykosociale faktorer;
- Studier som anvender epidemiologiske og statistiske metoder som tager højde for *healthy worker* effekten.

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13. Formidlings aktiviteter

2016

November – poster præsentation den nordiske konference om arbejdstid (*Working Hours in the Nordic Countries*, WINC-WOW), Stockholm

2017

Januar – poster præsentation på AMFF Årsmøde, København

Februar – mundtlig præsentation for Yngre Lægers Arbejds miljøudvalg, Lægeforeningen, København

Marts – mundtlig præsentation på møde med følgegruppen bestående af repræsentanter fra Danske Regioner, Dansk Sygeplejeråd, Lægeforeningen – Yngre Læger, Jordemoderforeningen, Dansk Erhverv, 3F og FOA, København

August – mundtlig præsentation på den internationale epidemiologiske konference (*International Epidemiology in Occupational Health*, EPICOH), Edinburgh

Oktober – mundtlig præsentation på den nordiske konference om arbejdstid (*Working Hours in the Nordic Countries*, WINC-WOW), Oslo

November – mundtlig præsentation på Arbejds miljøkonferencen, Nyborg

2018

Januar – mundtlig præsentation på workshop *Payroll Data in Shiftwork Research* (XIMES), Wien

Marts – mundtlig præsentation på møde med følgegruppen bestående af repræsentanter fra Danske Regioner, Dansk Sygeplejeråd, Lægeforeningen – Yngre Læger, Jordemoderforeningen, Dansk Erhverv, 3F og FOA, København

April – publikation af den første videnskabelige artikel om forhøjet blodtryk og svangerskabsforgiftning i tidsskriftet *Scandinavian Journal of Work, Environment & Health*

April – mundtlig præsentation på Årsmøde for Dansk Selskab for Arbejds- og Miljømedicin (DASAM), Nyborg

April – mundtlig præsentation på NIVA-kursus: *Occupational Hazards and Reproductive Health*, Malmø

Maj – mundtlig præsentation på NIVA-kursus: *Working Hours and Health*, København

Maj – poster præsentation på den nordiske konference om arbejdstid (*Working Hours in the Nordic Countries*, WINC-WOW), København

Oktober – nyheds artikel udgivet af Videncenter for Arbejds miljø, NFA, MitArbejds miljø.dk (<https://mitarbejds miljo.dk/artikler/nattevagter-oeger-risiko-svangerskabsforgiftning>).

Denne artikel dannede efterfølgende grundlag for en række artikler i diverse medier som for eksempel Fagbladet 3F (<https://fagbladet3f.dk/artikel/gravide-risikerer-forgiftning-af-natarbejde>); Dansk Sygeplejeråd (<https://dsr.dk/politik-og-nyheder/nyhed/nattevagter-oeger-risiko-for-svangerskabsforgiftning>); Avisen.dk (<https://www.avisen.dk/forbund-overrasket-sygeplejersker-boer-hvile-i-28-ti-533090.aspx>); Dansk Industri (<http://di.dk/Personale/Arbejdsmiljoe/Nyheder/Pages/Natarbejde-oeger-risiko-for-gravide.aspx?login=true>); FOA (<https://www.foa.dk/afdelinger/sosu/nyheder/global/news/afdelingsnyheder/sosu/2019/blad-2-2019/helbredet-betaler-prisen>); Propatienter.dk (<https://propatienter.dk/nyheder/1647-nattevagter-kan-skade-gravidens-helbred.html>); Ugebrevet A4.dk (<https://www.ugebreveta4.dk/artikel-print/sygeplejersken-catrine-godt-arbejdsmiljoe-er-en-lur-og-laenestole-paa-nattevagter>); Armoni.dk – kliniske vejledninger for Arbejds- og Miljømedicinere (http://www.armoni.dk/sites/default/files/Armoni_Fildeling/files/Public/Gravide/gravid_og_arbejdstid_2018.pdf); Sundhedspolitisk Tidsskrift (<https://sundhedspolitisktidsskrift.dk/nyheder/1402-nattevagter-kan-skade-gravidens-helbred.html>).

December – Ph.d.-afhandling sendt til Københavns Universitet

2019

Januar – mundtlig præsentation på møde med følgegruppen bestående af repræsentanter fra Danske Regioner, Dansk Sygeplejeråd, Lægeforeningen – Yngre Læger, Jordemoderforeningen, Dansk Erhverv, 3F og FOA, København

Januar – publikation af den anden videnskabelige artikel om sygefravær i tidsskriftet *Journal of Occupational & Environmental Medicine*

Januar – mundtlig præsentation på Forskningsmøde på Fertilitetsklinikken, Rigshospitalet

Marts – i forbindelse med publikation af artiklen om ufrivillig abort, blev resultaterne fra studierne om sygefravær, forhøjet blodtryk og svangerskabsforgiftning også omtalte i en række nationale og internationale medier som for eksempel Videnskab.dk (<https://videnskab.dk/krop-sundhed/gravide-med-natarbejde-faar-oftere-spontane-aborter>); Ugeskrift for Læger (<http://ugeskriftet.dk/nyhed/bare-nattevagter-giver-risiko-spontan-abort-ugen-efter>);

Marts – interview på "Go' morgen Danmark", TV2; telefon interview Ritzau;

Marts – mundtlig præsentation på statusmøde for DAD-følgegruppe, NFA

April – Ph.d.-forsvar, Bispebjerg Hospital, med udgivelse af fakta ark med opsummering af de publicerede resultater

April – Artiklen om fødselsdepression er under revision hos et videnskabeligt tidsskrift.

Der er endvidere planlagt:

Maj – mundtlig præsentation på den nordiske konference om arbejdstid (*Working Hours in the Nordic Countries*, WINC-WOW), København; Juni – mundtlig præsentation på Fødeafdelingen, Hvidovre Hospital; dato ikke fastlagt endnu – mundtlig præsentation for Yngre Lægers Arbejds miljøudvalg, Lægeforeningen, København; statusartikel i Ugeskrift for Læger om natarbejde og graviditet.

14. Bilag

Bilag 1 – Fakta ark, NFA

”Flere helbredsrisici for gravide med mere end 1 nattevagt om ugen”

Flere helbredsrisici for gravide med mere end 1 nattevagt om ugen

Gravide ansatte i sundhedssektoren med mere end 1 nattevagt om ugen har øget risiko for enten at miste deres foster eller blive syge. Det viser resultater af flere nye studier.

Hovedresultaterne fra projekterne 'PREGNIGHT' og 'Skiftarbejde og Helbred' viser, at

- gravide med mere end 1 nattevagt pr. uge har øget risiko for ufrivillig abort den efterfølgende uge.
- gravide med mere end 3 nattevagter i træk har større risiko for at få forhøjet blodtryk og svangerskabsforgiftning. Svært overvægtige gravide er særligt udsatte.
- gravide med nattevagter, især nattevagter på over 12 timer, har større risiko for at melde sig syge uafhængigt af andre faktorer.
- 1 nattevagt pr. uge øger sandsynligvis ikke risikoen for ufrivillig abort.
- op til 1 nattevagt pr. uge i gennemsnit i de første 20 graviditetsuger øger sandsynligvis ikke risikoen for forhøjet blodtryk og svangerskabsforgiftning, hvis man ikke har mere end 3 nattevagter i træk eller er svært overvægtig.

Forskerne har undersøgt sammenhængen mellem natarbejde og graviditetskomplikationer blandt cirka 20.000 gravide ansatte i de 5 regioner i Danmark. I undersøgelsen anvendes data fra 2007 til 2015, og de fleste arbejdede som læger eller sygeplejersker på hospitaler.

Forskerne anser resultaterne for meget troværdige, dels fordi de er baseret på et landsdækkende studie over flere år, hvor forskerne er sikre på, at udsættelse for natarbejde forekommer før helbredseffekterne, og dels



Forskerne har undersøgt sammenhængen mellem natarbejde og graviditetskomplikationer blandt cirka 20.000 gravide.

fordi der er tale om data af høj kvalitet om arbejdstider fra Dansk Arbejdstids-Database.

Forhøjet blodtryk og svangerskabsforgiftning

Et af hovedresultaterne viser, at gravide med flere end 3 nattevagter i træk havde ca. 40 procent øget risiko for forhøjet blodtryk og svangerskabsforgiftning. Det svarer til, at der, er 4,7 tilfælde af forhøjet blodtryk og svangerskabsforgiftning blandt 100 gravide, som har flere end 3 nattevagter i træk i de første 20 graviditetsuger. Til sammenligning er der 3,3 tilfælde af forhøjet blodtryk eller svangerskabsforgiftning pr. 100 gravide, som kun har 1 nattevagt af gangen og ikke flere i træk.

Svært overvægtige gravide kvinder – dvs. gravide med et Body Mass Index (BMI) på 30 kg/m² eller mere – har en væsentlig forøget risiko for at udvikle forhøjet blodtryk og svangerskabsforgiftning. Sammenlignet med andre

svært overvægtige kvinder finder forskerne en 4 til 5-dobling af risikoen for forhøjet blodtryk og svangerskabsforgiftning blandt svært overvægtige gravide, der i løbet af de første 20 graviditetsuger arbejder på én af følgende måder:

- mere end 1 nattevagt om ugen
- nattevagter, som varer 12 timer eller mere
- mere end 3 nattevagter i træk
- møder på arbejdet mindre end 28 timer efter en nattevagt mindst 5 gange.

Den øgede risiko svarer til mindre end 5 ekstra tilfælde af forhøjet blodtryk og svangerskabsforgiftning blandt 100 svært overvægtige gravide med de pågældende arbejdstider.

Forskerne fandt ingen øget risiko blandt gravide, der i gennemsnit har mere end 1 nattevagt om ugen i løbet af de første 20 graviditetsuger med

mindre arbejdet er tilrettelagt, så de har mere end tre nattevagter i træk, eller hvis de er svært overvægtige.

Ufrivillig abort

Forskerne fandt også en sammenhæng mellem natarbejde og ufrivillig abort, der viser, at jo flere nattevagter, jo højere risiko for ufrivillig abort. Det understøtter resultater fra tidligere studier, som viser, at der er forhøjet risiko for abort for gravide med fast natarbejde. Som noget nyt viser forskerne, at dette også gælder for gravide med færre antal nattevagter fx blandt skiftarbejdere med både dag- og nattevagter.

Resultaterne viser en øget risiko for ufrivillig abort, hvis man har mere end 1 nattevagt om ugen - særligt efter 8. graviditetsuge. Det svarer til, at der blandt 100 gravide, der har mere end én nattevagt om ugen, er 5,5 tilfælde af ufrivillige aborter fra den 9. til den 22. graviditetsuge. Til sammenligning er der 4,2 tilfælde af ufrivillige aborter blandt kvinder, som kun har dagvagter.

Sygemelding

Endelig fandt forskerne, at nattevagter, især lange nattevagter på mere end 12 timer, øger risikoen for at melde sig syg med 55 procent i de to døgn, der følger efter nattevagten. Resultatet er uafhængigt af faktorer som fx alder, jobtitel og socioøkonomisk status. Det øgede sygefravær efter lange nattevagter svarer til, at der er 4,3 sygemeldinger pr. 100 lange nattevagter i løbet af de første 32 graviditetsuger. Til sammenligning er der 2,8 sygemeldinger pr. 100 dagvagter. Disse resultater stemmer overens med tidligere studier.

Dansk ArbejdstidsDatabase (DAD)

DAD giver forskerne adgang til detaljerede og præcise informationer om, hvornår kvinderne arbejder i løbet af deres graviditet, fordi:

- DAD indeholder oplysninger om daglige komme- og gåtider for alle ansatte i de danske regioner – hovedsageligt ansatte inden for sundheds-væsenet.
- Registeret dækker perioden 2007-15 og opdateres løbende.
- DAD indeholder mere end 250.000 ansattes arbejdstid og er det største register af sin slags i verden.

Kroppens mørkehormon - melatonin

Kroppens mørkehormon, melatonin, spiller muligvis ind på risikoen for ufrivillig abort, forhøjet blodtryk og svangerskabsforgiftning. Melatonin bliver produceret i koglekirtlen i hjernen og hjælper med at tilpasse kroppens rytme til døgnets lys- og mørkecyklus. Produktionen af melatonin hæmmes af lys, og man udskiller derfor mindre melatonin, når man arbejder om natten. Studier tyder på, at melatonin kan være afgørende for, om man har en uproblematiske og sund graviditet.

Samarbejdspartnere

Studiet er gennemført på Arbejds- og Miljømedicinsk Afdeling, Bispebjerg/Frederiksberg Hospital i samarbejde med Det Nationale Forskningscenter for Arbejds miljø (NFA) og en række andre forskningsinstitutioner:

- Københavns Universitet
- Kræftens Bekæmpelse
- Dansk Ramazzini Center, Aarhus Universitetshospital
- Fertilitetsklinikken – Rigshospitalet
- Region Hovedstadens Psykiatri.

Finansiering

Projekterne 'PREGNIGHT' og 'Skiftarbejde og Helbred' er finansieret af Arbejds miljø-forskningsfonden.

Yderligere oplysninger

- Læge, ph.d.-studerende Paula EC Hammer, Arbejds- og Miljømedicinsk Afdeling, Bispebjerg/Frederiksberg Hospital, paulahammer@dadlnet.dk.
- Professor Anne Helene Garde, NFA, ahg@nfa.dk.

Videnskabelige publikationer om resultaterne

- Hammer P, Flachs E, Specht I et al. Night work and hypertensive disorders of pregnancy: A national register-based cohort study. *Scandinavian Journal of Work, Environment and Health* 2018;44(4):403-413. doi: 10.5271/sjweh.3728

- Hammer PEC, Garde AH, Begtrup LM et al. Night work and sick leave during pregnancy: A national register-based within-worker cohort study [Epub ahead of print]. *Occupational and Environmental Medicine* 2019. doi: 10.1136/oemed-2018-105331
- Begtrup LM, Specht IO, Hammer PEC et al. Night work and miscarriage: A Danish nationwide register-based cohort study

[Epub ahead of print]. *Occupational and Environmental Medicine* 2019. doi: 10.1136/oemed-2018-105592 doi: 10.5271/sjweh.3728

- Hammer PEC. *Night work during pregnancy and maternal health – The PREGNIGHT project*. Ph.D. thesis, Arbejds- og Miljømedicinsk Afdeling, Bispebjerg/Frederiksberg Hospital, 2019.



Bilag 2 – Videnskabelig artikel vedrørende studie I om forhøjet blodtryk
og svangerskabsforgiftning



Original article

Scand J Work Environ Health [Online-first -article](#)

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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.

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[2015;41\(3\):219-324](#) [2013;39\(4\):321-426](#) [2010;36\(2\):81-184](#)
[1989;15\(6\):0](#) [2007;33\(4\):241-320](#) [2006;32\(6\):413-528](#)

Key terms: [circadian disruption](#); [cohort study](#); [gestational hypertension](#); [hypertension](#); [hypertensive disorder](#); [night work](#); [payroll data](#); [preeclampsia](#); [pregnancy](#); [register-based cohort study](#); [shift work](#); [shift worker](#); [work schedule](#); [working time](#)

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](#).



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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}

Hammer P, Flachs E, Specht I, Pinborg A, Petersen S, Larsen A, Hougaard K, Hansen J, Hansen Å, Kolstad H, Garde A, Bonde JP. Night work and hypertensive disorders of pregnancy: a national register-based cohort study. *Scand J Work Environ Health* – online first. doi:10.5271/sjweh.3728

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

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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).

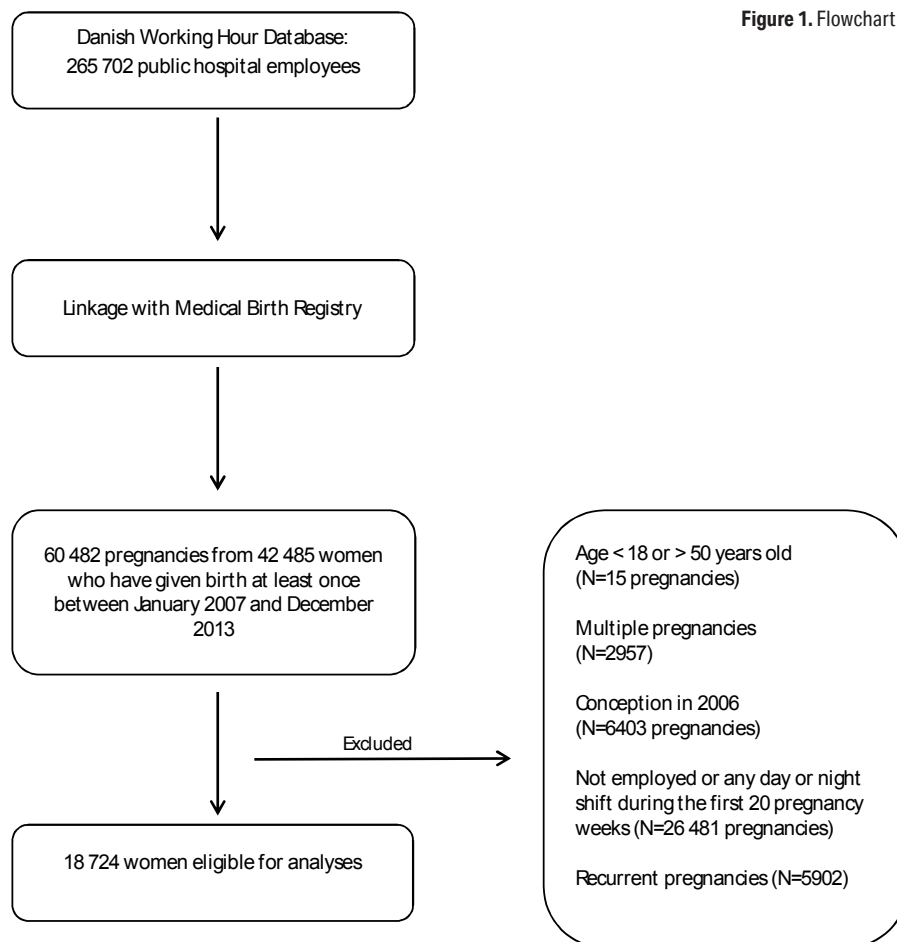
Shifts, including on-call shifts, lasting ≥ 3 hours were defined as day (start time after 06:00 and end time before 21:00 hours), evening (end time after 21:00 and before 02:00 hours), night (any start and end time including working hours between 23:00 and 06:00 hours) and early morning (start time between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



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–I15), 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/m ²)			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/m² revealed that those who worked ≥4 consecutive night shifts had substantially increased risk of HDP compared to day workers (OR 5.31, 95% CI 1.98–14.22). The corresponding risk for women with BMI <25 kg/m² 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/m²) 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-

sure. 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 pathophysiology 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

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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.

Bilag 3 – Videnskabelig artikel vedrørende studie II om sygefravær

ORIGINAL ARTICLE

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

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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 9799 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, that is, 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 with day shifts during all pregnancy trimesters. The risk was highest for night shifts lasting >12 hours (OR 1.37, 95% CI 1.15 to 1.63 for nurses; OR 1.87, 95% CI 1.69 to 2.08 for physicians) and among women aged >35 years (OR 1.42, 95% CI 1.24 to 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.

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 policies 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}

Key messages

What is already known about this subject?

► 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.

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.

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 organisation of their working schedules may reduce sick leave during pregnancy.

To our knowledge, there are no studies on short-term (≤ 14 consecutive days) sick leave during pregnancy. It is possible that short-term 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-year 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 hypothesised that night shifts lead to lack of recovery and where 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 (DWH), 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 was 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 DWH 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 ($n=2957$) and pregnancies conceived in 2006 ($n=6403$), 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 DWH, started after conception or ended before 32 pregnancy weeks ($n=16 570$) to ensure that payroll data were 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 ($n=1714$ pregnancies excluded), leaving 9799 women eligible for analyses (online supplementary figure).

Exposure

Risk days were days with a DWH 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 DWH 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/m²), parity (1, 2, ≥ 3) and smoking (non-smoker, 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 to 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 organisations of working schedules and work content, that is, 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 ORs with 95% CIs.

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 V.9.4 software (SAS Institute, Cary, North Carolina, USA).

RESULTS

The study cohort comprised 9799 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

Table 1 Characteristics of 9799 pregnant public hospital employees* in Denmark, 2007–2013

	N	%	Mean	SD
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†				
All women			60.7	25.4
Nurses			57.5	22.1
Physicians			80.5	24.3
Number of night shifts†				
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†				
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†				
All women			31.6	38.7
Nurses			34.4	38.9
Physicians			15.7	25.9

*Workers with ≥1 day shift and ≥1 night shift and ≥1 day of sick leave during the first 32 pregnancy weeks.

†During the first 32 pregnancy weeks.

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

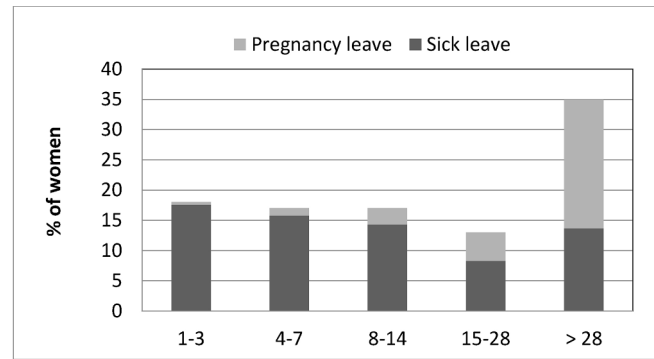


Figure 1 Distribution of total days of absence, including sick leave and pregnancy leave, during the first 32 pregnancy weeks among 9799 public hospital employees* in Denmark, 2007–2013. *Workers with ≥1 day shift and ≥1 night shift and ≥1 day of sick leave during the first 32 pregnancy weeks.

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). 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 with 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 second and third trimesters. These women had slightly higher proportion of overweight and obesity and of medium and low SES compared with 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.

We found increased OR of calling in sick within 24 hours after night versus day shifts in all pregnancy trimesters (OR 1.28, 95% CI 1.19 to 1.37 in the first trimester; OR 1.27, 95% CI 1.17 to 1.39 in the second trimester and OR 1.13, 95% CI 0.96 to 1.31 in the third trimester)—see table 2. Physicians presented the highest estimates (OR 1.94, 95% CI 1.67 to 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 to 1.29.

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 to 1.63) among women older than 35 years; 1.25 (95% CI 1.17 to 1.35) among women aged 30–35 years and 1.16 (95% CI 1.08 to 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 to 1.69 among all women; OR 1.37, 95% CI 1.15 to 1.63 among nurses and OR 1.87, 95% CI 1.69 to 2.08 among physicians)—see table 3. Analysis of night shifts of ≤8 and >8–12 hours among physicians

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* among 9799 public hospital employees† in Denmark, 2007–2013

	Risk days (n)	OR	95% CI
First pregnancy trimester			
All women	197 851	1.28	1.19 to 1.37
Nurses (n=6334)	124 091	1.14	1.05 to 1.24
Physicians (n=1593)	40 252	1.94	1.67 to 2.27
Second pregnancy trimester			
All women	182 838	1.27	1.17 to 1.39
Nurses	111 665	1.02	0.91 to 1.15
Physicians	40 496	1.89	1.59 to 2.26
Third pregnancy trimester			
All women	93 649	1.13	0.96 to 1.33
Nurses	53 257	1.01	0.81 to 1.25
Physicians	24 965	1.49	1.09 to 2.04

*Fixed effects logistic regression analysis.

†Workers with ≥1 day shift and ≥1 night shift and ≥1 day of sick leave during the first 32 pregnancy weeks.

revealed relatively higher estimates, but they were based on quite few shifts (table 3).

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 second and third 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

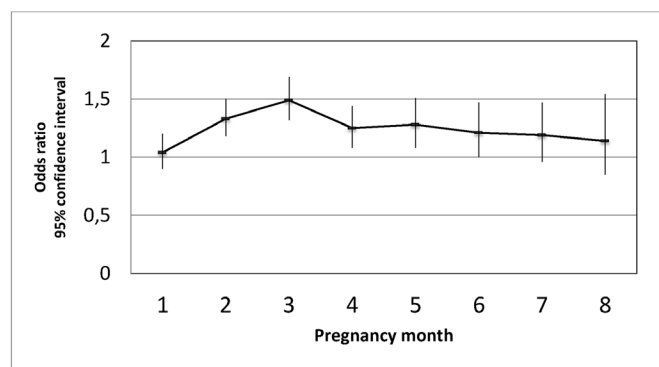


Figure 2 Risk of calling in sick, regardless of duration of sick leave, within 24 hours after night versus day shifts during the first 32 pregnancy weeks stratified by pregnancy month with the participants as their own controls* among 9799 public hospital employees† in Denmark, 2007–2013. *Fixed effects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

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

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

*Workers with ≥1 day shift and ≥1 night shift and ≥1 day of sick leave during the first 32 pregnancy weeks.

†Fixed effects logistic regression analysis.

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 to 1.9 adjusted for age, occupation, full-time 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 (HR 1.61, 95% CI 1.42 to 1.83), and a trend of increasing risk with increasing number of monthly night shifts (HR 1.89, 95% CI 1.67 to 2.15 among women with >8 night shifts per pregnancy month). Last, 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, either those with fixed night, fixed evening or with fixed day shifts, it is possible that this rate is underestimated.

Our findings of higher risk of sick leave following night shifts during first 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 first 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 first trimester followed by a relative decrease during the second and third 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 third 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 first pregnancy trimester, that is, before the healthy worker selection has occurred. Nevertheless, even women who worked night shifts until the third 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 where 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 first trimester for sensitivity analysis including pregnancy leave (OR 1.27, 95% CI 1.19 to 1.35) and main analysis (OR 1.28, 95% CI 1.19 to 1.37—from [table 1](#)), but attenuation of the estimates in the second and third 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 and in the organisation of shift work. Nurses had higher rates of absence (see [table 1](#)), especially during the first trimester, and higher proportion of absence periods lasting >14 days (46%) and >28 days (31%) compared with physicians (27% and 16%, respectively). Consequently, relatively more physicians than nurses contributed to analyses of the second and third 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 2 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 are 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 accounts 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 organisation of their working schedules may reduce sick leave during pregnancy.

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Contributors PECH, JPB, AHG, EMF, ADL and LMB provided substantial contributions to the conception of the study and the analysis of the data. PECH,

AHG and ADL contributed to the acquisition of the data. PECH 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.

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Competing interests None declared.

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