Afslutningsrapport til Arbejdsmiljøforskningsfonden

Skifteholdsarbejde og risiko for hjerte-karsygdomme og brystkræft, en 10 års opfølgningsundersøgelse baseret på daglige registreringer af arbejdstid

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Forord

Tidligere forskning har vist, at natarbejde øger risikoen for hjertekarsygdomme og brystkræft. Mange af disse studier er baseret på udetaljerede selvrapporterede oplysninger om arbejdstid og er derfor afhængig af deltagernes evne til at genkalde sig natarbejde mange år tilbage i tid. Størstedelen af den tidligere forskning har koncentreret sig om varigheden af natarbejde i form af antal år med natarbejde, og få har undersøgt om det er en sammenhæng mellem antallet af nattevagter eller intensiteten af natarbejde og risikoen for hjertekarsygdom eller brystkræft.

Vi ansøgte derfor om midler fra Arbejdsmiljøforskningsfonden for at efterprøve resultaterne af den internationale forskning i en dansk kontekst, hvor de unikke danske registre gav mulighed for præcist at opgøre den enkelte medarbejders eksponering for natarbejde og risiko for hjertekarsygdomme og brystkræft.

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Dansk resumé

Formål: Formålet med denne undersøgelse var at undersøge om skifteholdsarbejde inklusive aften- og natarbejde øger risikoen for hjertekarsygdom og brystkræft samt undersøge validiteten af selvrapporterede oplysninger om tidligere natarbejde.

Materiale og metoder: Undersøgelsen omfatter 4 studier. Studie I og II er register-baserede kohortestudier, studie III er et valideringsstudie og studie IV er en tilnærmelse (emulering) til et randomiseret forsøg baseret på omfattende registerdata. Alle 4 studier er baseret på data fra Dansk Arbejdstids Database som indeholder dag-for-dag oplysninger om arbejdstid for samtlige 343.620 ansatte ved de 5 danske regioner mellem 2007/2008 og 2020. I 2015/2016 indsamlede vi selvrapporterede oplysninger om livsstilsfaktorer og tidligere regelmæssigt natarbejde blandt alle aktuelt ansatte ved 3 af 5 danske regioner. En række nationale registre fra Danmarks Statistik og Sundhedsdatastyrelsen samt Kvalitetsdatabasen for Brystkræft (DBCG) leverede oplysninger om forekomsten af hjertekarsygdom og brystkræft.
I studie I undersøgte vi sammenhængen mellem mængden, intensiteten og varigheden af natarbejde og risikoen for hjertekrampe eller blodprop i hjertet. Studiet var baseret på samtlige ansatte mellem 2007/2008 og 2015. I studie II undersøgte vi sammenhængen mellem mængden af nattevagter og risikoen for blodprop i hjertet blandt nyansat sundhedspersonale fra deres første aften- eller nattevagt i perioden 2008/2009 til 2020. I studie III undersøgte vi validiteten af selvrapporteret regelmæssigt natarbejde blandt kvinder med og uden en tidligere brystkræft diagnose. Vi undersøgte hvilken betydningen en eventuel forskel i validiteten mellem de 2 grupper havde for vurderingen af risikoen for brystkræft efter natarbejde. I studie IV undersøgte vi betydningen af langvarigt natarbejde med mindst 12 nattevagter pr. år blandt kvindelige sygeplejersker, jordemødre, læger, social- og sundhedshjælpere og -assistenter, portører og rengøringspersonale ansat mellem 2007/2008 og 2020.

Resultater: Studiepopulationerne bestod af (I) 254.031 dag- og natarbejdere, (II) 137.184 nyansatte aften- og natarbejdere, (III) 225 brystkræft patienter og 1800 matchede kontroller samt (IV) 105.096 kvindelige ansatte der skiftede til natarbejde eller forblev i dagarbejde.
Studie I fandt ingen sammenhæng mellem mængden, intensiteten eller varigheden af natarbejde og risikoen for hjertekrampe eller blodprop i hjertet. Studie II fandt ingen sammenhæng mellem mængden af aften- og natarbejde og risikoen for blodprop i hjertet. Studie III fandt at kvinder med en tidligere brystkræft diagnose lidt bedre huskede deres tidligere regelmæssige natarbejde end kvinder uden tidligere brystkræft, og at denne forskel medførte en lille overvurdering af sammenhængen mellem natarbejde og risikoen for brystkræft. Studie IV fandt samme risiko for brystkræft blandt kvinder i natarbejde som for kvinder i dagarbejde efter 6 års opfølgning, men tegn på en fordoblet risiko blandt natarbejdere efter 12 år. Det sidste resultat er dog behæftet med stor statistisk usikkerhed da få kvinder forblev ansat i natarbejde i hele 12 års perioden.

Konklusion: Dette projekt kan ikke dokumentere, at en reduktion af mængden, intensiteten eller varigheden af natarbejde vil reducere risikoen for hjertekrampe eller blodprop i hjertet. Vi fandt ingen dosis-responssammenhænge mellem mængden, intensiteten eller varigheden af natarbejde og hjertekarsygdom, hvilket er helt centralt for kausale sammenhænge. Tidligere studier baseret på selvrapporterede oplysninger om natarbejde kan have overvurderet sammenhængen mellem brystkræft og natarbejde. Projektet gave visse holdepunkter for en fordoblet risiko efter 12 års kontinuerligt natarbejde med mindst 12 nattevagter per år.

English summary

Aim: The aims of this project were to examine the risk of coronary heart disease, myocardial infarction and breast cancer following evening or night shift work using day by day payroll data on day, evening and night shifts, and to examine the validity of self-reported night shift work and estimate the consequences of any misclassification.

Materials and methods: This project was based on four studies: two register-based cohort studies (study I and II), a validation study (study III), and an emulated target trial (study IV). All four studies were based on the Danish Working Hour Database which contains day by day payroll-based information on working time for all 343,620 health care workers with all Danish hospital regions since 2007/2008. A 2015/2016 survey among currently employed workers in 3 of 5 hospital regions provided self-reported information on lifestyle factors (smoking, body mass index, alcohol consumption, and diurnal preference) and previous regular night shift work. Several Danish nationwide registries supplied data on hospital diagnosed coronary heart disease, myocardial infarction, breast cancer and relevant register-based confounders.

The first cohort study (I) examined the exposure-response relations between several night work characteristics (ever, monthly, cumulative, year of rotating night shift, years of night shift, and consecutive night shifts) and risk of coronary heart disease among all health care workers 2007/2008-2015. The second cohort study (II) examined the exposure-response relations between cumulative evening and night shifts and myocardial infarction among all newly hired evening and night shift health care workers 2008/2009-2020. The validation study (III) examined if breast cancer status affected the validity of self-reported regular night shift work as reported in the 2015/2016 survey compared to payroll-based information on night shifts according to the Danish Working Hour database 2007/2008-2015. Quantitative bias analyses were used to examine the consequences of any misclassification. The emulated target trial (IV) aimed to examine the effect of long-term sustained night shift work on breast cancer occurrence, based on all women health care professionals 2007/2008-2020. The analysis focused on women shifting from day work to night shift work with an intensity of at least 12 night shifts per year for up to 12 years.

Results: The study populations for the four studies included (I) 254,031 day- and night shift workers, (II) 137,184 newly hired evening and night shift workers, (III) 225 breast cancer patients and 1800 matched controls, and (IV) 105,096 day workers that shifted to night shift work (≥12 night shifts per year) or remained in day work.
In study I we observed no consistent exposure-response relations by any of the night shift work characteristics and coronary heart disease among night shift workers. In study II we observed no exposure-response relations between cumulative evening and night shifts and myocardial infarction among newly hired men and women evening and night shift health care workers.
In the validation study (III) we found that women breast cancer patients had a slightly better recall of their previous regular night shift work compared with controls but a similar specificity, which in the quantitative bias analysis were shown to lead to a small overestimation of the association between night shift work and breast cancer, based on a hypothetical study population.

In the emulated target trial study (IV), women health care professionals that shifted to night shift work had the same risk of breast cancer as day workers after 6 years, but a doubled risk after 12 years, however, based on few night workers adhering to night shift work for full 12 years.

Conclusion: This project does not indicate that reducing extent of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shift and consecutive night shifts will reduce the risk of coronary heart disease. It showed no exposure-response relation, a key characteristic of causal effects, between cumulative evening and night shifts and incident myocardial infarction. Previous case-control studies relying on retrospective recall of night shift exposure may have slightly overestimated the association between breast cancer and night shift work. The project indicated a doubled risk of breast cancer following 12 years of sustained night shift work with an intensity of ≥12 night shifts per year.

Baggrund

Skifteholdsarbejde og natarbejde

Skifteholdsarbejde og natarbejde er væsentlig for det moderne samfund, hvor mange industrier og servicefag er afhængige af at arbejde udføres 24 timer i døgnet, 365 dage om året. I Europa er ca. 18% af arbejdsstyrken ansat i skifteholdsarbejde, mens 18% af mænd og 10% af kvinder arbejder om natten.[1]

Forskning i 1970'erne og 1980'erne undersøgte en mulig sammenhæng mellem skifteholdsarbejde, natarbejde og hjertekarsygdomme med blandede resultater.[2, 3] Nyere systematiske reviews er generelt enige om, at skifteholdsarbejdere og natarbejdere har en ca. 20% forøget risiko for hjertekarsygdomme sammenlignet med dagarbejdere.[4-8] Disse reviews er dog baseret på meget forskelligartede studier med en række metodemæssige svagheder som selv-rapporteret arbejdstid, utilstrækkelig inddragelse af potentielle confoundere og få studier, der undersøger dosis-respons sammenhænge.

I 1990'erne og først i 2000-tallet blev skifteholdsarbejde udpeget som en mulig risikofaktor for brystkræft.[9-11] I 2010 klassificerede International Agency for Research of Cancer (IARC) skifteholdsarbejde, der medfører døgnrytmeforstyrrelser, som sandsynligvis kræftfremkaldende for mennesker.[12] Baseret på yderligere forskning konkluderede IARC i 2020, at natarbejde sandsynligvis er kræftfremkaldende for mennesker.[13] Disse konklusioner var baseret på stærk mekanistisk evidens, tilstrækkelig evidens fra dyrestudier, men kun begrænset evidens fra studier af mennesker på grund af forskelligartede fund.[13] Herudover led studierne af mennesker af de samme metodemæssige begrænsninger som beskrevet tidligere for hjertekarsygdomme.

Mekanismer

Døgnrytmeforstyrrelser efter skifteholdsarbejde og natarbejde er blevet foreslået som værende årsag til hjertekarsygdomme og brystkræft.[13-15] Menneskets døgnrytme forstyrres af lyset på arbejdspladsen når arbejdet finder sted udenfor de almindelige dagtimer, hvorved vi ikke kan følge vores naturlige døgnrytme.[15] Menneskets døgnrytme reguleres af lys og mørke, hvilket påvirker produktionen af hormonet melatonin. Melatonin beskrives ofte som et søvn-hormon, og det frigives primært i kroppen om natten. Når vi er udsat for lys om natten undertrykkes produktionen af melatonin.[16, 17] Melatonin menes at have en beskyttende effekt på kræft[17] og spiller muligvis også en rolle i forebyggelse af hjertekarsygdomme.[18]

Skifteholdsarbejde og natarbejde leder til utilstrækkelig eller forstyrret søvn, eksempelvis kortere søvn eller dårligere søvnkvalitet. [14, 19] Undersøgelser blandt danske sygeplejersker [20] og politibetjente [21] har fundet at søvn efter nattevagter var kortere og af ringere kvalitet sammenlignet med søvn på dage med dagarbejde. Kort nattesøvn er blevet betegnet som en risikofaktor for hjertekarsygdomme gennem forøget appetit og overvægt,[22] og dermed kan skifteholdsarbejde og natarbejde potentielt påvirke kostvaner, vægt og kolesterolniveau i blodet. Alkoholforbrug og fysisk aktivitet ser dog ud til ikke at være påvirket af skifteholdsarbejde og

natarbejde.[15] Rygning er rapporteret oftere set blandt skifteholds- og natarbejdere.[5]

Projektets formål

De nationale danske sundhedsregistre kombineret med Dansk Arbejdstids Database[23] gør det muligt for os at studere skifteholdsarbejde, natarbejde, hjertekarsygdomme og brystkræft i en stor kohorte på 343.620 ansatte i det regionale sundhedsvæsen mellem 2007 og 2020. Den særlige kombination af registerbaserede oplysninger om både eksponering og udfald samt en stor studiepopulation gør det muligt for denne undersøgelse at bidrage til den samlede viden på området. Herudover gør en spørgeskemaundersøgelse fra 2015-2016 blandt 65.000 aktuelt ansatte ved regionerne det muligt for os, at undersøge validiteten af selvrapporterede oplysninger om natarbejde sammenlignet med objektive oplysninger om arbejdstid fra regioneners lønsystemer.

Formålet med denne undersøgelse var derfor at undersøge dosis-respons sammenhænge mellem skifteholdsarbejde, natarbejde og hjertekarsygdomme og brystkræft, samt at undersøge validiteten af selvrapporterede oplysninger om regelmæssigt natarbejde sammenlignet med objektive individuelle lønsystem-baserede oplysninger om nattevagter.

Metoder

Studiedesign

Fire studier indgår i projektet (Tabel 1)

Tabel 1. Oversigt over studier i projektet

	Study I	Study II	Study III	Study IV
Title	Night shift work characteristics and risk of incident coronary heart disease among health care workers: national cohort study	Working evening and night shifts in the health care sector and incidence of myocardial infarction: a national cohort study in Denmark	Validity of self-reported night shift work among women with and without breast cancer	The effect of long-term night shift work on risk of breast cancer among women healthcare workers: a target trial emulation
Design	Cohort study	Cohort study	Validation study	Emulated target trial
Source population	All Danish health care workers of all Danish public hospitals 2007/2008-2015	All newly hired health care workers of all Danish public hospitals with evening or night shift work 2008/2009-2020	All health care workers of all Danish public hospitals employed 2015/2016 in 3 of 5 Danish hospital regions who responded to the questionnaire	All women health care professional workers (nurses, physicians, midwives, auxiliary nurses, janitors, and orderlies) of all Danish public hospitals employed in day work 2007-2020

Exposure	Night shift work	Evening- and night shift work	Night shift work	Night shift work
Exposure assessment	Day/night worker, monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shifts, consecutive night shifts	Cumulative evening and night shifts, cumulative night shifts, cumulative evening shifts, monthly evening and night shift work	Register-based and self-reported ever night shift work	Day work or ≥12 night shifts per year
Outcome	Coronary heart disease	Myocardial infarction	Breast cancer	Breast cancer
Covariates accounted for	age, diabetes, obesity, hypercholesterolemia, hypertension, family history of cardiovascular disease, calendar year, occupation and educational level	age, diabetes, obesity, hypercholesterolemia, hypertension, family history of cardiovascular disease, calendar year, and education	Age, alcohol consumption, shift work status	Covariates defined at year 1: age, occupation, obesity, family history of breast cancer or ovarian cancer, treatment for alcohol overconsumption, age at first child, parity, oral contraception, hormone replacement therapy, other sex hormones, and participation in the breast cancer screening program. Time-varying covariates included the year 1 covariates and additionally education and ever receiving 4 weeks of sickness benefits
Statistical analysis	Poisson regression	Poisson regression	Sensitivity, specificity, quantitative bias analysis	Logistic regression

Studiepopulation

Alle fire studier er baseret på ansatte ved de danske regioner mellem 2007 og 2020 fra database Dansk Arbejdstids Database[23].

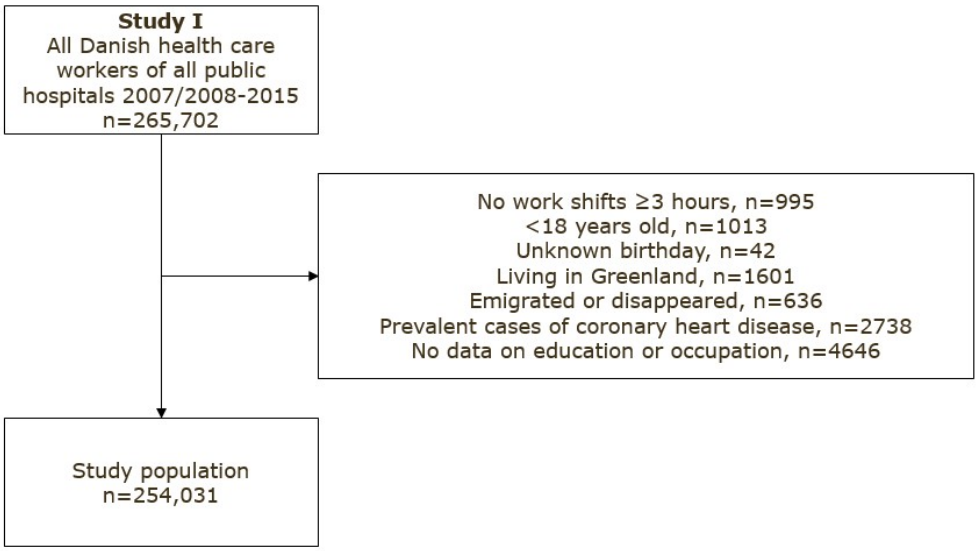

Figure 1. Flowchart of study I

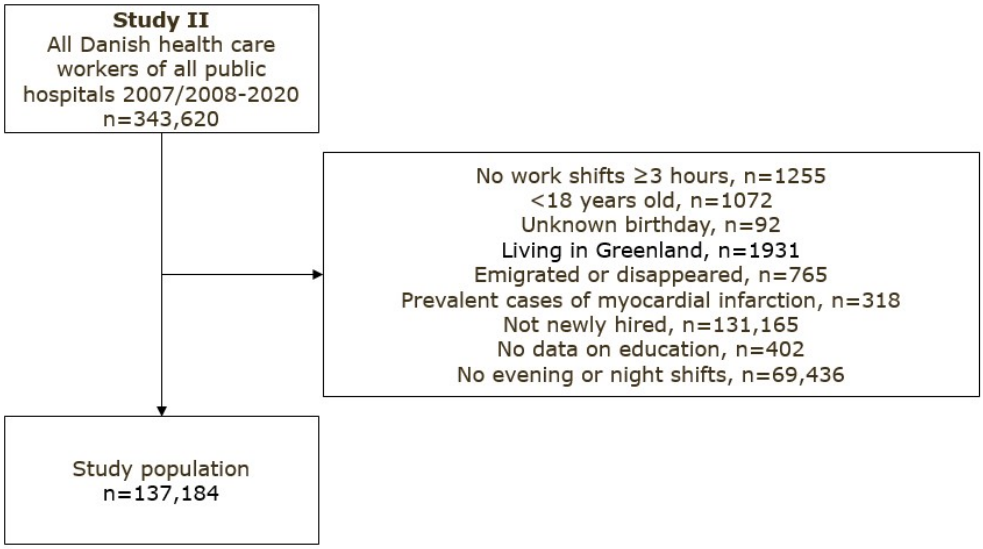

Figure 2. Flowchart of study II

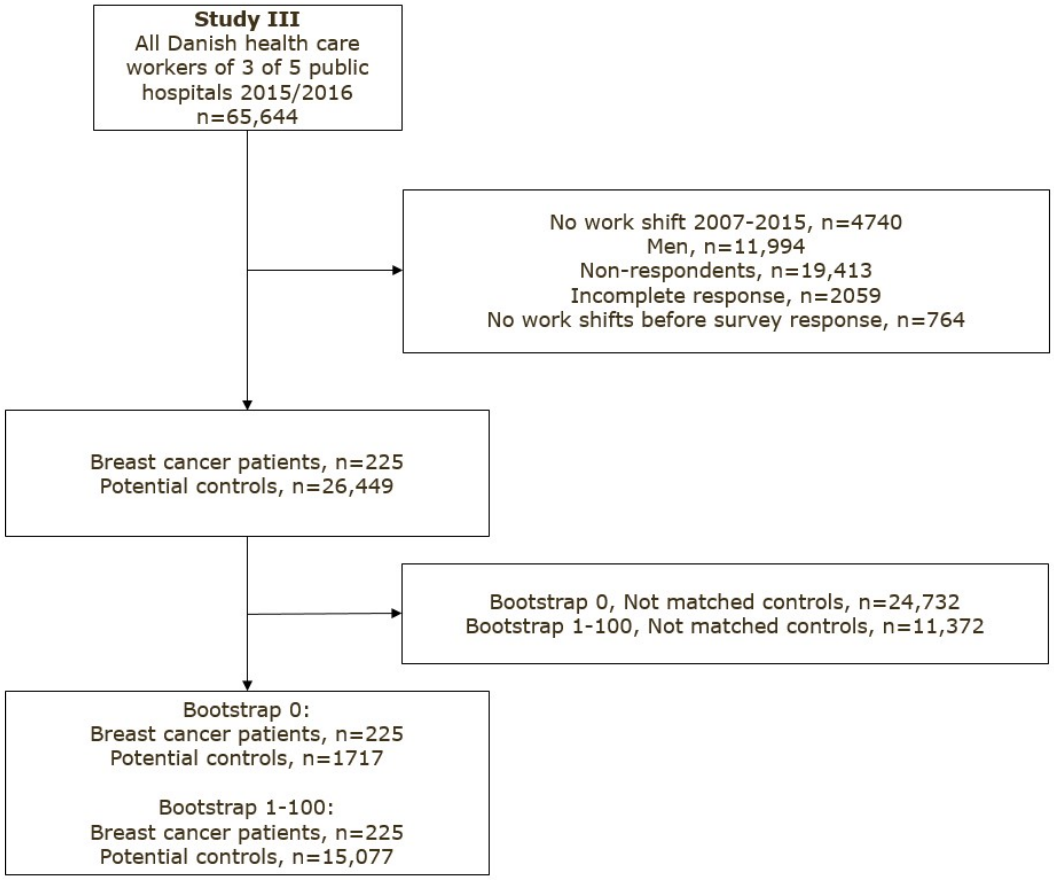

Figure 3. Flowchart of study III

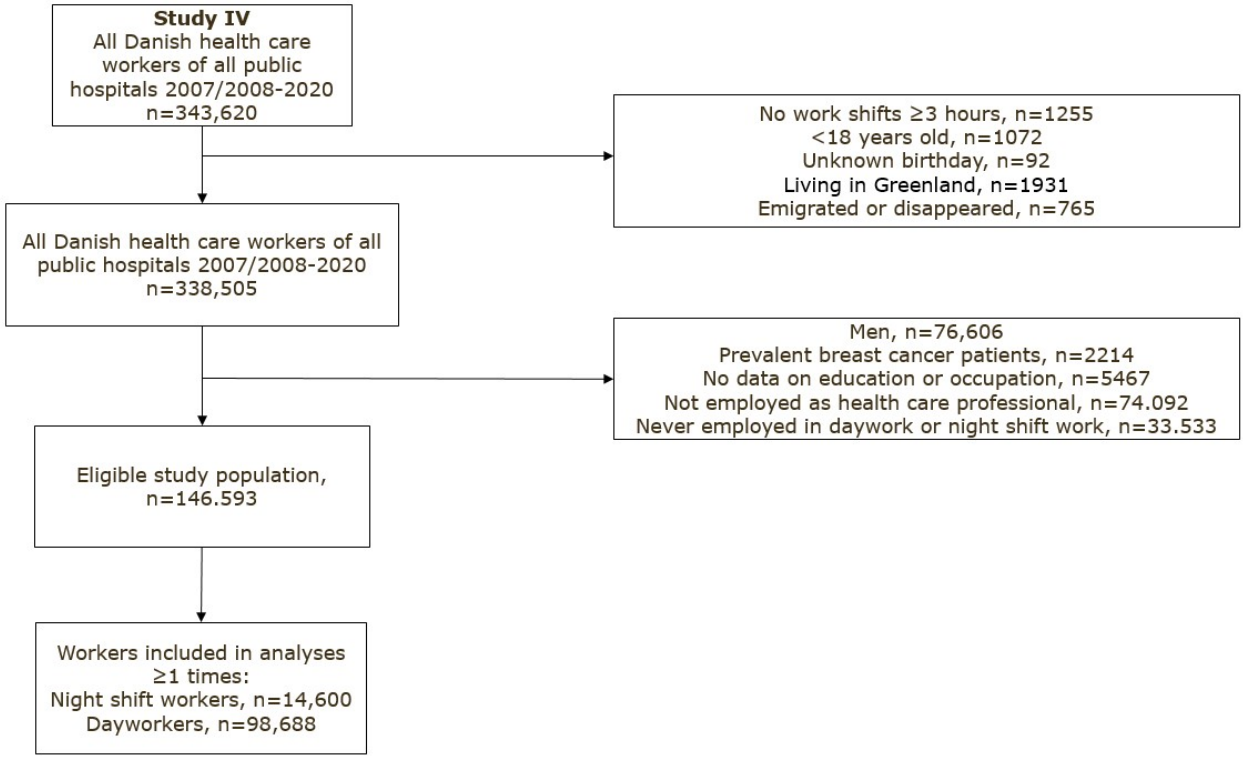

Figure 4. Flowchart of study IV

Eksponering

Eksponeringen i projektet er baseret på registerbaserede oplysninger om aften- og natarbejde i Dansk Arbejdstidsdatabase[23] (studie I, II, III, IV) samt selvrapporterede oplysninger om natarbejde i en spørgeskemaundersøgelse foretaget blandt 65.644 aktuelt ansatte ved 3 af de 5 danske regioner i slutningen af 2015 (studie III).

I studie I baserede vi eksponeringsvurderingen på antallet af nattevagter i opfølgningsperioden. Eksponeringen blev opgjort som:

- Dag- eller nat arbejder
- Gennemsnitligt antal nattevagter pr. måned
- Kumuleret antal nattevagter
- Antal år med skifteholdsarbejde
- Antal år med natarbejde
- Længste ubrudte periode af nattevagter

I studie II baserede vi eksponeringsvurderingen på antallet af aften- og nattevagter i opfølgningsperioden. Eksponeringen blev opgjort som:

- Kumuleret antal aften- og nattevagter
- Kumuleret antal nattevagter
- Kumuleret antal aftenvagter
- Gennemsnitligt antal aften- og nattevagter pr. måned

I studie III baserede vi eksponeringsvurderingen på selvrapporteret natarbejde fra 2015 spørgeskemaundersøgelsen samt registerbaseret natarbejde baseret på Dansk Arbejdstidsdatabase. Eksponeringen blev i begge datakilder opgjort som

- Tidligere natarbejde (ja/nej)

I studie IV baserede vi eksponeringsvurderingen på antallet af nattevagter i opfølgningsperioden. Eksponeringen blev opgjort som:

- Dagarbejde
- Kontinuerligt natarbejde (≥12 nattevagter pr. år)

Udfald

Udfaldet i de 4 studier var baseret på registeroplysninger om hjertekarsygdomme (studie I og II) og brystkræft (studie III og IV). Oplysninger om hjertekarsygdomme blev indhentet fra Landspatientregistret og suppleret med dødsårsagsregistret, mens oplysninger om brystkræft blev indhentet fra Kvalitetsdatabasen for Brystkræft (DBCG) og Cancerregistret.

Tabel. Oversigt over udfaldsdiagnoser

	ICD-7	ICD-8	ICD-10
Studie I		410, 413	I20, I21
Studie II		410	I21
Studie III	170.0-170.5		C50
Studie IV	170.0-170.5		C50

Potentielle confoundere

Vi indsamlede registerbaserede oplysninger om en række potentielle confoundere til studie I, II og IV: køn, alder, diabetes, overvægt, forhøjet blodtryk, forhøjet kolesterol, hjertekarsygdom i familien, årstal, beskæftigelse, uddannelse, brystkræft og kræft i æggestokkene i familien, behandling for alkohol overforbrug, alder ved første barnefødsel, antal børnefødsler i alt, brug af p-piller, hormonbehandling, brug af andre kønshormoner samt deltagelse i brystkræft screeningsprogrammet for kvinder mellem 50 og 69 år.

I studie III indsamlede vi registerbaserede oplysninger om alder og natarbejde samt spørgeskemabaserede oplysninger om alkoholforbrug. Disse blev brugt til matchning af kvinder med en tidligere brystkræft diagnose til kvinder uden brystkræft.

Statistisk analyse

I studie I fulgte vi ansatte ved de Danske regioner fra første registrerede vagt, tidligst 2007 (4 regioner) eller 2008 (1 region), indtil koronar hjertesygdom, død, udvandring, forsvinden eller followup sluttede 31/12 2015.

I studie II fulgte vi nyansatte ved de Danske regioner fra første registrerede aften- eller nattevagt, tidligst 2008 (4 regioner) eller 2009 (1 region), indtil blodprop i hjertet, død, udvandring, forsvinden eller followup sluttede 31/12 2020.

I studie I og II blev eksponerings-respons sammenhænge analyseret ved hjælp af Poisson regression. For hvert eksponeringsmål blev hver dag i followup perioden

inddelt i kategorier baseret på fordelingen af persontid. I studie I udgjorde de ikke-eksponerede referencegruppen, og i studie II udgjorde de lavest eksponerede aften og natarbejdere referencegruppen.

I studie III inkluderede vi kun kvinder der deltog i spørgeskemaundersøgelsen i 2015-2016. Vi undersøgte validiteten af deres selvrapporterede tidligere natarbejde ved at sammenholde disse oplysninger med registerbaserede oplysninger om arbejdstiden for den samme periode. Vi beregnede sensitivitet (andelen der rapporterede sandt natarbejde) og specificitet (andelen der rapporterede sandt dagarbejde) for både kvinder med og uden en tidligere brystkræft diagnose. Vi anvendte herefter kvantitativ bias analyse til at undersøge konsekvensen af forskelle i evnen til korrekt at rapportere tidligere natarbejde mellem de to grupper for epidemiologiske studier af sammenhængen mellem natarbejde og brystkræft.

Studie IV tilnærmede (emulerede) et randomiseret forsøg, hvor kvinder ansat i dagarbejde ved de danske regioner mellem 2008 og 2019 blev opdelt i 2 grupper: én gruppe fortsatte i dagarbejde og den anden skiftede til natarbejde med en intensitet på mindst 12 nattevagter om året. Data blev analyseret som 'intention-to-treat' hvor vi undersøgte effekten af at blive randomiseret til at forblive i dagarbejde sammenholdt med at skifte til natarbejde. Data blev også analyseret som 'per-protocol', hvor vi kun fulgte de ansatte så længe de forblev i den arbejdsplan de var blevet tildelt ved forsøgets start. De ansatte blev fulgt indtil brystkræft diagnose, død, udvandring, forsvinden eller followup sluttede 31/12 2020.

Resultater

Studie I

Night shift work characteristics and risk of incident coronary heart disease among health care workers: national cohort study

Vi identificerede 3326 nye tilfælde af koronar hjertesygdom blandt 254.031 mænd og kvinder i løbet af opfølgningsperioden. Natarbejdere arbejdede i gennemsnit 1.7-1.8 nattevagter om måneden. Vi fandt ingen stigning i risiko for koronar hjertesygdom med stigende intensitet, mængde, varighed eller længste periode af nattevagter for hverken mænd eller kvinder.

Studie II

Working evening and night shifts in the health care sector and incidence of myocardial infarction: a national cohort study in Denmark

Vi identificerede 476 nye tilfælde af myokardie infarkt i løbet af opfølgningstiden blandt 137.184 nyansatte mænd og kvinder fulgt fra første aften- eller nattevagt. Vi fandt ingen stigning i risiko for myokardieinfarkt med stigende mængde af aften og/eller natarbejde for hverken mænd eller kvinder.

Studie III

Validity of self-reported night shift work among women with and without breast cancer

Vi inviterede i 2015 65.644 aktuelt ansatte ved 3 af 5 danske regioner til at deltage i en spørgeskemaundersøgelse om blandt andet tidligere natarbejde og alkoholforbrug og 27.438 kvinder besvarede de relevant spørgsmål i tilstrækkelig grad til at kunne inkluderes i studiet. Blandt respondenterne identificerede vi 225 med en brystkræft diagnose stillet før deltagelse i spørgeskemaundersøgelsen, og vi koblede hver af disse med 8 kontroller fri for brystkræft.

Ansatte med en tidligere brystkræft diagnose var bedre til at huske deres tidligere natarbejde end ansatte uden en brystkræft diagnose (sensitivitet 86.2 mod 80.6), og i kvantitativ bias analyse fandt vi at denne forskel i rapportering i epidemiologiske studier vil lede til en lille overvurdering af styrken af sammenhængen mellem natarbejde og risiko for brystkræft.

Studie IV

The effect of long-term night shift work on risk of breast cancer among women healthcare workers: a target trial emulation

Vi identificerede 105.096 kvindelige ansatte i dagarbejde og emulerede et randomiseret forsøg hvor disse enten forblev i dagarbejde eller skiftede til langvarigt natarbejde. I løbet af 12 års opfølgning identificerede vi 1321 nye tilfælde af brystkræft. Projektet gave visse holdepunkter for en fordoblet risiko efter 12 års kontinuerligt natarbejde med mere end 12 nattevagter per år.

Konklusioner

Dette projekt fandt ingen dosis-responssammenhænge mellem natarbejde og risiko for koronar hjertesygdom. Ligeledes fandt vi ingen dosis-responssammenhænge mellem aften- og/eller natarbejde og risiko for myokardieinfarkt.

Dette projekt har også vist, at kvinder med en tidligere brystkræft diagnose er en smule bedre til at huske deres tidligere natarbejde, og at denne misklassifikation kan lede til en overestimering af sammenhængen mellem natarbejde og brystkræft i epidemiologiske studier af brystkræft baseret på selvrapporterede oplysninger om natarbejde.

Slutteligt har projektet fundet visse holdepunkter for en fordoblet risiko for brystkræft efter 12 års kontinuerligt natarbejde med mindst 12 nattevagter per år.

Perspektiver

Dette projekt finder i studie I ikke, at en reduktion af intensitet, mængde eller varighed af natarbejde, vil lede til en reduktion af koronar hjertesygdom og vi kan derfor ikke på baggrund af dette projekt anbefale ændringer i tilrettelæggelsen af natarbejde mhp. at forebygge hjertesygdom.

Vi fandt i studie II ingen dosis-responssammenhænge, hvilket er et centralt kriterium for årsagssammenhænge, mellem mængden af aften og/eller natarbejde og myokardieinfarkt hvilket stiller spørgsmål ved om tidligere studier, som har fundet denne sammenhæng, afspejler årsagssammenhænge.

Vores valideringsstudie, studie III, tyder på at epidemiologiske studier baseret på retrospektivt indsamlede selvrapporterede oplysninger om natarbejde kan have overestimeret sammenhængen med brystkræft.

Dette projekt fandt i studie IV visse holdepunkter for en forøget risiko for brystkræft efter langvarigt kontinuerligt natarbejde med en intensitet på 12 eller flere nattevagter pr. år, og en begrænsning af intensitet eller varighed af natarbejde kunne potentielt have en beskyttende effekt mod brystkræft. Studiets resultater er dog usikre, og flere analyser er nødvendige for at give konkrete anbefalinger.

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Populærvidenskabelig artikel

Får man hjertesygdomme eller brystkræft af at arbejde om aftenen eller natten?

Projekt: Skifteholdsarbejde og risiko for hjerte-kar sygdomme og brystkræft, en 10 års opfølgningsundersøgelse baseret på daglige registreringer af arbejdstid

Bevillingshaver: Arbejds- og Miljømedicin, Aarhus Universitetshospital

Resume: Aften- og natarbejde er udbredt i en række brancher og tidligere studier har vist, at der blandt aften- og natarbejdere er forøget risiko for hjertesygdom og brystkræft. Mange af disse studier er dog baseret på spørgeskemaoplysninger om arbejdstiden, hvilket medfører at oplysningerne om mange års arbejdstid ofte kan have været udetaljerede og vanskelige at huske for deltagerne. Der er brug for studier baseret på store grupper af aften- og natarbejdere fulgt gennem lang tid baseret på præcise oplysninger om antal aften- og nattevagter og forekomsten af hjertesygdom og brystkræft. Samtidig er det også vigtigt at undersøge om den rapporterede sammenhæng mellem natarbejde og brystkræft helt eller delvist kan forklares med forskelle i deltagernes evne til at huske tidligere natarbejde. Det bør også undersøges, om evnen til at huske tidligere natarbejde er forskellig for kvinder med og uden en tidligere brystkræft diagnose. I dette projekt fandt vi ingen sammenhæng mellem mængden, intensiteten eller varigheden af natarbejde og risikoen for hjertekrampe eller blodprop i hjertet. Vi fandt at tidligere studier baseret på spørgeskemaoplysninger om arbejdstid kan have overvurderet sammenhængen mellem natarbejde og brystkræft. Endelig fandt vi tegn på en fordobling af risiko for brystkræft efter 12 års natarbejde, men dette estimat er forbundet med stor usikkerhed.

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Får ansatte ved de danske offentlige hospitaler hjertesygdomme eller brystkræft af aften- og natarbejde?

Aften- og natarbejde er udbredt i en række brancher, eksempelvis ved de offentlige hospitaler. Her varetages døgnet rundt væsentlige patient-relaterede opgaver af blandt andet læger, sygeplejersker, jordemødre, rengøringsassistenter, portører, social- og sundhedshjælpere og assistenter. Aften og natarbejde kan mange steder ikke undgås, så det er vigtigt arbejdet tilrettelægges, så de ansatte ikke bliver syge af deres arbejde.

Tidligere studier har vist, at der blandt aften- og natarbejdere er en forøget risiko for hjertesygdom og brystkræft. En central svaghed ved mange af disse studier er dog, at man har baseret oplysninger om arbejdstiden på spørgeskemaer, hvor det kan være vanskeligt at indfange detaljer om mange års skiftende aften- og natarbejde. Samtidig vil vi forvente at kvinder med brystkræft er mere opmærksomme på deres tidligere aften- og natarbejde. I det omfang dette er sket, kan det have skævvredet resultaterne i disse studier.

For at undgå denne potentielle skævvridning, har vi i disse studier indhentet præcise og detaljerede dag-for-dag oplysninger om aften- og natarbejde fra de danske regioners lønsystemer og koblet dette med højkvalitetsdata fra danske sundhedsregistre om hjertesygdom og brystkræft.

Projektet bestod af 4 delstudier:

Natarbejde og hjertekrampe og blodprop i hjertet.
I dette studie inkluderede vi samtlige 250.000 personer ansat ved de danske regioner mellem 2007 og 2015. Vi undersøgte om der var en sammenhæng mellem mængden, intensiteten og varigheden af natarbejdet og risikoen for hjertekrampe og blodprop i hjertet. Vi fandt ikke, at var højere risiko for hjertekrampe og blodprop i hjertet blandt ansatte med mange nattevagter, høj intensitet eller mange års natarbejde sammenlignet med ansatte med få nattevagter, lav intensitet eller få års natarbejde.

Aften og natarbejde blandt nyansatte og blodprop i hjertet
Dette studie inkluderede samtlige 137.000 nyansatte ved de danske regioner mellem 2008 og 2020 som vi fulgte fra deres første aften- eller nattevagt. Vi undersøgte om der var en sammenhæng mellem antallet af nattevagter og risikoen for blodprop i hjertet. Resultaterne viste, at der ikke var højere risiko for blodprop i hjertet blandt ansatte med mange nattevagter sammenlignet med ansatte med få nattevagter.

Validitet af selvrapporteret natarbejde
I dette studie inkluderede vi regionalt ansatte der i 2015 deltog i en spørgeskemaundersøgelse om tidligere natarbejde. For alle deltagere havde vi adgang til oplysninger om ansattes arbejdstid dag-for-dag fra regionernes lønsystemer 2007-2015. Vi undersøgte hvor præcist 225 kvinder med en brystkræft diagnose rapporterede tidligere natarbejde, sammenlignet med 1800 kvindelige kontroller uden brystkræft. Vi fandt at kvinderne med brystkræft var bedre til at huske deres tidligere natarbejde end kontrollerne, og at dette kan have medført at studier baseret på spørgeskema oplysninger om arbejdstid kan have overvurderet sammenhængen mellem natarbejde og risiko for brystkræft.

Langvarigt natarbejde og risiko for brystkræft
Med dette studie ønskede vi at undersøge blandt kvindelige sundhedsfaglige ansatte med dagarbejde ved de danske regioner mellem 2008 og 2020, om et skifte til langvarigt natarbejde ville øge risikoen for brystkræft. Studiet blev gennemført som et simuleret randomiseret forsøg, hvor vi anvendte data fra de danske sundhedsregistre til at undersøge hvordan det kunne være gået de ansatte hvis de skiftede til natarbejde sammenlignet med hvis de forblev i dagarbejde. Vi fandt visse holdepunkter for, at kvinder som havde haft vedvarende natarbejde med minimum 12 nattevagter per år i en 12-årig periode havde en potentielt fordoblet risiko for brystkræft. Estimaterne var dog forbundet med stor usikkerhed.

Konklusion
Vi fandt i disse studier ingen evidens for en sammenhæng mellem mængden, intensiteten eller varigheden af natarbejde og risikoen for hjertekrampe eller blodprop i hjertet. Vi fandt også, at tidligere studier baseret på spørgeskema oplysninger om arbejdstid kan have overvurderet sammenhængen mellem natarbejde og brystkræft. Endelig fandt vi visse holdepunkter for en fordoblet risiko efter 12 års kontinuerligt natarbejde med mindst 12 nattevagter per år.

Afslutning på projekt

Indsendes til:
forskningsfonden@at.dk

Generelle oplysninger om projektet

1	**Projektets titel**
	Skifteholdsarbejde og risiko for hjerte-karsygdomme og brystkræft, en 10 års opfølgningsundersøgelse baseret på daglige registreringer af arbejdstid

2	**Ansøger**	
	CVR-nummer:	29762929
	Institutionens navn:	Aarhus Universitetshospital, Arbejds- og Miljømedicin
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3	**Ansvarlig projektleder/kontaktperson**	
	Navn:	Henrik A. Kolstad
	Arbejdssted:	Aarhus Universitetshospital, Arbejds- og Miljømedicin
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	Tlf.nr.:	7845 0900
	e-mail:	henkol@rm.dk

4	**Projektet formål og hovedhypoteser** (Kortfattet beskrivelse af projektets formål og hovedhypoteser herunder begrundelse for evt. ændringer i formål og hovedhypoteser):
	Hovedhypoteser Mange befolkningsundersøgelser har vist forøget risiko for hjerte-karsygdomme og brystkræft blandt personer med natarbejde og andre former for skifteholdsarbejde. Men der er begrænset viden om hvad varighed og intensitet af forskellige arbejdstidsmønstre betyder for risikoen for disse sygdomme. Skifteholdsarbejde kan ikke undgås, og denne viden er en forudsætning for, at vi kan tilrettelægge skifteholdsarbejde så sikkert som muligt.

Et flertal af hidtidige undersøgelser har brugt selv-udfyldte spørgeskemaer til at måle arbejdstid. Men spørgeskemaer kan vanskeligt fange detaljerede arbejdstidsmønstre og ændringer i disse over tid. De risikerer også at give skævvredne resultater, hvis de indsamles fra deltagerne efter at de er blevet syge. Tilsammen kan dette have betydet, at man både har overset reelle sammenhænge og fundet sammenhænge, som ikke er reelle.
Vores hypotese var, at der var en risiko for, at personer som allerede er blevet syge havde en bedre eller en anden erindring af deres arbejdstidsmønstre, end personer som ikke er blevet syge.

Formål
Det overordnede formål var at undersøge sammenhængen mellem skifteholdsarbejde og risikoen for hjertekarsygdomme og brystkræft. Vi ville undersøge betydningen af varighed og intensitet af forskellige arbejdstidsmønstre, vores hypotese var, at der var en dosis-respons sammenhæng, Vi ville også undersøge om der er særligt sårbare persongrupper og risikoen for specifikke hjerte-kar- og brystkræftsygdomme.

Da vi i projektet havde adgang til samtidige oplysninger om selvrapporteret tidligere natarbejde og lønregisterbaserede oplysninger om natarbejde, valgte vi at undersøge validiteten af selvrapporteret natarbejde blandt kvinder med og uden tidligere brystkræft.

5 **Resultater og videnskabelig nyhedsværdi** (Redegør for de videnskabelige resultater af projektet og deres nyhedsværdi. Redegør desuden for hvilke resultater der var forventede henholdsvis uventede. Hvordan forholder resultaterne sig til øvrige forskningsresultater?):

Studie I havde til formål at undersøge dosis-respons sammenhænge mellem intensitet og mængden af natarbejde og risiko for hjertekrampe eller blodprop blandt samtlige 254.031 ansatte ved alle danske offentlige hospitaler mellem 2007 og 2015. Studiet fandt ingen sammenhæng mellem mængden, intensiteten eller varigheden af natarbejde og risikoen for hjertekrampe eller blodprop i hjertet.

Studie II havde til formål at undersøge dosis-respons sammenhænge mellem mængden af aften- og natarbejde og risiko for blodprop i hjertet blandt 137.184 nyansatte ved alle danske offentlige hospitaler mellem 2008 og 2020, fulgt fra første aften eller nattevagt. Studiet fandt ingen sammenhæng mellem mængden af aften- og natarbejde og risikoen for blodprop i hjertet.

Studie III havde til formål at undersøge validiteten af selvrapporteret natarbejde blandt 225 kvinder med og 1800 alders-matchede kvinder uden en brystkræft diagnose. Studiet fandt at kvinder med en tidligere brystkræft diagnose huskede lidt bedre deres tidligere regelmæssige natarbejde end kvinder uden tidligere brystkræft, og at denne forskel medførte en overvurdering af sammenhængen mellem natarbejde og risikoen for brystkræft.

Studie IV havde til formål at undersøge risikoen for brystkræft efter langvarigt natarbejde blandt 105.096 kvinder, der skiftede til natarbejde eller forblev i dagarbejde. Studiet fandt samme risiko for brystkræft blandt kvinder i natarbejde som for kvinder i dagarbejde efter 6 års opfølgning, men tegn på en fordoblet risiko blandt natarbejdere efter 12 år. Det sidste resultat er dog behæftet med statistisk usikkerhed da få kvinder forblev ansat i natarbejde i hele 12 års perioden.

6 **Arbejdsmiljøperspektiver (**Hvilken relevant viden er der skabt i projektet? Hvilken betydning har det for arbejdsmiljøet og arbejdsmiljøarbejdet? Kan projektets resultater omsættes til praktisk anvendelse for målgrupperne? Hvordan kan resultaterne overføres til andre målgrupper?)

Vi kan ikke dokumentere, at en reduktion af mængden, intensiteten eller varigheden af natarbejde vil reducere risikoen for hjertekrampe eller blodprop i hjertet. Vi fandt ingen dosis-responssammenhænge mellem mængden, intensiteten eller varigheden af natarbejde og hjertekarsygdom, hvilket er centralt kriterium for kausale sammenhænge. Tidligere epidemiologiske studier baseret på retrospektivt indsamlede selvrapporterede oplysninger om natarbejde kan have overestimeret sammenhængen medbrystkræft. Denne undersøgelse fandt visse holdepunkter for en forøget risiko for brystkræft efter langvarigt kontinuerligt natarbejde med en intensitet på 12 eller flere nattevagter pr. år, og en begrænsning af intensitet eller varighed af natarbejde kunne potentielt have en beskyttende effekt mod brystkræft. Studiets resultater er dog usikre, og flere analyser er nødvendige for at give konkrete anbefalinger.

7	**Medarbejdere** (angiv navne på videnskabelige medarbejdere i projektet)
	1. Jesper Medom Vestergaard, Arbejds- og Miljømedicin, Aarhus Universitetshospital 2. Henrik Albert Kolstad, Arbejds- og Miljømedicin, Aarhus Universitetshospital 3. Annett Dalbøge, Arbejds- og Miljømedicin, Aarhus Universitetshospital 4. Anne Helene Garde, Det Nationale Forskningscenter for Arbejdsmiljø (NFA), København 5. Sadie Costello, Environmental Health Science, School of Public Health, University of California, Berkeley, USA 6. Jens Peter Ellekilde Bonde, Arbejds- og Miljømedicin, Bispebjerg og Frederiksberg Hospital 7. Johnni Hansen, Kræftens Bekæmpelse 8. Åse Marie Hansen, Institut for Folkesundhedsvidenskab, Københavns Universitet 9. Ann Dyreborg Larsen, Det Nationale Forskningscenter for Arbejdsmiljø (NFA), København 10. Mikko Härmä, Finnish Institute for Occupational Health, Finland 11. Morten Böttcher, Hjertesygdomme, Gødstrup Hospital, Herning 12. Jesper Nikolai Dietrich Haug, Aarhus Universitet 13. Morten Fenger-Grøn, Arbejds- og Miljømedicin, Aarhus Universitetshospital 14. Mathias Moselund Rønnow, Arbejds- og Miljømedicin, Gødstrup Hospital, Herning 15. Peer Christiansen, Institut for Klinisk Medicin - Plastik- og Brystkirurgi, Aarhus Universitetshospital, Aarhus

8	**Øvrige institutioner** (angiv øvrige institutioner som har deltaget i projektet)
	1. 2. 3.

9	**Interessentgruppe** (Angive navne på medlemmer af evt. interessentgruppe)
	Følgegruppen for Dansk Arbejdstidsdatabase (DAD), som omfatter repræsentanter fra alle regioner og Danske regioner NFAs følgegruppe for projekter i forskning om arbejdstid

10		
	Startdato for projektet:	01.01.2020
	Planlagt slutdato:	31.12.2022
	Faktisk slutdato:	31.12.2025

Formidling (Ved fortrolighed skal denne aftales med Arbejdsmiljøforskningsfondens sekretariat inden indsendelse af slutrapporten.)

11	**Populærformidling (mundtlig)**	
	Konferencer, seminarer m.v.:	Vestergaard, J.M., 2021-10-13 – Arbejdsmedicin, Aarhus Universitetshospital, Dansk Metal – mundtlig præsentation – "Natarbejde og risiko for iskæmisk hjertesygdom"
	Målgruppe for de væsentligste aktiviteter (max 5):	Vestergaard, J.M., 2022-05-02 – Arbejdsmiljøforskningsfondens Årskonference 2022 – poster præsentation – "Night Work and 9-year Risk of Coronary Heart Disease: a Cohort Study of Exposure Response Relations"
		1. Forskere 2. Fagforeninger 3. Sundhedspersonale 4. 5.

12	**Populærformidling (skriftlig)**	
	Projektets populær-videnskabelige artikel:	Får ansatte ved de danske offentlige hospitaler hjertesygdomme eller brystkræft af aften- og natarbejde?
	Øvrige artikler, nyheder m.v.: (Angiv titel og medie) **Hjemmeside/sociale medier:**	2023-11-20 Aarhus Universitet, pressemeddelelse, "New study: One week of night shifts per month does not increase the risk of coronary heart disease", https://health.au.dk/en/display/artikel/nyt-studie-en-uges-nattevagter-om-maaneden-oeger-ikke-risikoen-for-blodpropper-i-hjertet 2023-11-20 Linked-in.com, "New study shows no increased risk of coronary heart disease after night shift work", https://health.au.dk/en/display/artikel/nyt-studie-en-uges-nattevagter-om-maaneden-oeger-ikke-risikoen-for-blodpropper-i-hjertet 2025-06-24 Graduate School of Health, Aarhus University, "Press release: Ph.d. defence Jesper Medom Vestergaard" (ikke længere tilgængelig på Aarhus Universitets hjemmeside) 2025-06-24 ramazzini.dk, "Velkommen til Jesper Medom Vestergaards ph.d.-forsvar", https://ramazzini.dk/dk/ph.d.forsvarjespermedomvestergaard

13	**Videnskabelig formidling (mundtlig)**
	Oplæg på konference, seminarer m.v. (angiv konference og titel på oplæg): Vestergaard, J.M., 2019-06-07 - Arbejdsmedicin, Aarhus Universitetshospital – mundtlig præsentation – ”Skifteholdsarbejde og blodprop i hjertet: et kohorte studie med komme-gå-tider”

Vestergaard, J.M., 2019-11-27 - 3rd Annual Research Meeting 2019 – poster præsentation – "Shift work and 9-year risk of myocardial infarction: a cohort study of payroll data"

Vestergaard, J.M., 2020-03-19 – WINC 2020 Helsinki – mundtlig præsentation – "Number of recent night shifts and risk of coronary event"

Vestergaard, J.M., 2020-06-26 – Arbejdsmedicin, Aarhus Universitetshospital – mundtlig præsentation – "Night shifts and risk of coronary heart disease among nurses, physicians and other health care workers: a national cohort study"

Vestergaard, J.M., 2020-10-02 – Arbejdsmedicin, Regionshospitalet Herning – mundtlig præsentation – "Night shifts and risk of coronary heart disease among nurses, physicians and other health care workers: a national cohort study"

Vestergaard, J.M., 2020-10-27 – Dansk Ramazzini Centers 9. årlige seminar – mundtlig præsentation – "Night shifts and risk of coronary heart disease among nurses, physicians and other health care workers: a national cohort study"

Vestergaard, J.M., 2020-11-12 - WOW consortium Internal Meeting 11-12th november 2020 – mundtlig præsentation – "Night shifts and risk of coronary heart disease among nurses, physicians and other health care workers: a national cohort study"

Vestergaard, J.M., 2021-09-16 - DASAM årsmøde 2021 16-17 september 2021 – mundtlig præsentation – "Night Work Characteristics and Incidence of Coronary Heart Disease: Exposure-response Relations"

Vestergaard, J.M., 2021-09-21 – OMEGAnet Training School – mundtlig præsentation – "The immediate risk of myocardial infarction following night shift work: the impact of changes in day-by-day working hour patterns"

Vestergaard, J.M., 2021-10-25 – EPICOH 2021 – mundtlig præsentation – "Night Work Characteristics and Incidence of Coronary Heart Disease: Exposure-response Relations"

Vestergaard, J.M., 2022-04-01 – Arbejdsmedicin, Aarhus Universitetshospital – mundtlig præsentation – "Shift work and risk of cardiovascular disease, breast cancer and depression"

Vestergaard, J.M., 2022-05-16 – Working Hours and Health, Helsinki – mundtlig præsentation – "Night work as trigger of Myocardial Infarction"

Vestergaard, J.M., 2022-10-04 – Arbejdsmedicin, Aarhus Universitetshospital (with external Research Professor Karin Broberg) – mundtlig præsentation – "Shift work and risk of cardiovascular disease, breast cancer and depression"

Vestergaard, J.M., 2023-01-20 – Aarhus Universitet, PhD Day – mundtlig præsentation – "Myocardial infarction incidence rates among night workers in the Danish health care sector: exposure-response relations"

Vestergaard, J.M., 2023-01-27 – Arbejdsmedicin, Aarhus Universitetshospital – mundtlig præsentation – "Night work and myocardial infarction – exposure-response relations"

Vestergaard, J.M., 2023-01-27 – Arbejdsmedicin, Aarhus Universitetshospital – mundtlig præsentation – "Validity of self-reported night work"

Vestergaard, J.M., 2023-03-14 – EPICOH 2023 – mundtlig præsentation – "Myocardial infarction rates following night work: exposure-response relations"

Vestergaard, J.M., 2023-05-10 – GRASPH Summer School – mundtlig præsentation – "Shift work and risk of cardiovascular disease, breast cancer and depression, a 14-year follow-up study of payroll data"

Vestergaard, J.M., 2023-11-22 – NFA Arbejdstidsgruppe – mundtlig præsentation – "Validity of self-reported night shift work among women with and without breast cancer"

Vestergaard, J.M., 2023-12-15 – Arbejdsmedicin, Gødstrup, projektkavalkade – mundtlig præsentation – ” Night shift work characteristics and risk of incident coronary heart disease among health care workers: national cohort study”

Vestergaard, J.M., 2023-12-15 – Arbejdsmedicin, Gødstrup, projektkavalkade – mundtlig præsentation – ” Validity of self-reported night shift work among women with and without breast cancer”

Vestergaard, J.M., 2024-01-19 – Aarhus Universitet, PhD Day 2024 – mundtlig præsentation – ” Validity of self-reported night shift work among women with and without breast cancer”

Vestergaard, J.M., 2024-03-05 - NFA Tirsdagsmøde – mundtlig præsentation – “Shift work and risk of cardiovascular disease and breast cancer, a 14-year follow-up study of payroll data”

Vestergaard, J.M., 2024-03-12 - Arbejdsmedicin, Aarhus Universitetshospital – mundtlig præsentation – ” Shift work and risk of cardiovascular disease and breast cancer, a 14-year follow-up study of payroll data”

Vestergaard, J.M., 2024-06-12 - NordicEpi 2024 København – mundtlig præsentation – “Validity of self-reported night shift work among women with and without breast cancer”

Vestergaard, J.M., 2024-09-11 - Staff Meeting, Aarhus Universitetshospital – mundtlig præsentation – ” Working evening and night shifts in the healthcare sector and incidence of myocardial infarction”

Vestergaard, J.M., 2024-11-05 - 7th Annual Research Meeting, Aarhus Universitetshospital – poster præsentation – “Evening & night shift work and myocardial infarction among Danish health care workers”

Vestergaard, J.M., 2025-05-12 - WINC2025 (Working Hours in the Nordic Countries) symposium – mundtlig præsentation – “The effect of long-term night shift work on risk of breast cancer among women healthcare workers”

Vestergaard, J.M., 2025-05-19 – KvanLab, Arbejdsmedicin, Gødstrup – mundtlig præsentation – ” The effect of long-term night shift work on risk of breast cancer among women healthcare workers – a target trial emulation”

Vestergaard, J.M., 2025-06-24 – Aarhus Universitetshospital, PhD Forsvar – mundtlig præsentation – ”Working evening and night shifts and risk of coronary heart disease, myocardial infarction, and breast cancer, a 14-year follow-up study of payroll data”

Vestergaard, J.M., 2025-10-06 - EPICOH 2025 – poster præsentation – “Working evening and night shifts in the health care sector and incidence of myocardial infarction: a national cohort study in Denmark”

Vestergaard, J.M., 2025-10-06 - EPICOH 2025 – mundtlig præsentation – “Working evening and night shifts in the health care sector and incidence of myocardial infarction: a national cohort study in Denmark”

Vestergaard, J.M., 2025-11-05 - Dansk Ramazzini Centers 14. årlige seminar – mundtlig præsentation – “The effect of long-term night shift work on risk of breast cancer among women healthcare workers: a target trial emulation”

Vestergaard, J.M., 2025-11-27 – NFA Følgegruppemøde for Dansk Arbejdstidsdatabase – mundtlig præsentation – ” Working evening and night shifts in the health care sector and incidence of myocardial infarction: a national cohort study in Denmark”

14	**Videnskabelig formidling (skriftlig)**

Peer reviewede artikler (angiv titel og tidsskrift m.v.):
1. “Night shift work characteristics and risk of incident coronary heart disease among health care workers: national cohort study”, International Journal of Epidemiology, 2023, https://doi.org/10.1093/ije/dyad126

	2. “Validity of self-reported night shift work among women with and without breast cancer”, Scandinavian Journal of Work, Environment and Health, 2024, https://doi.org/10.5271/sjweh.4142 **Øvrig skriftlig videnskabelig formidling (fx bogkapitler):** (Angiv titel og medie): 1. 2. 3.

15	**Projektansvarliges underskrift og dato** Undertegnede erklærer, at ovenstående oplysninger og oplysningerne i bilag er rigtige. Hvis der er afgivet urigtige eller vildledende oplysninger i ansøgningen, eller hvis oplysninger, som kan have betydning for afgørelse om tilsagn, er tilbageholdt, kan et tilsagn annulleres, og evt. udbetalinger kræves tilbagebetalt.
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Night shift work characteristics and risk of incident coronary heart disease among health care workers: national cohort study

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Abstract

Background: Night work has been associated with coronary heart disease. The present study examined exposure-response relations between quantitative night work characteristics and coronary heart disease (angina pectoris or myocardial infarction) with the aim to contribute to evidence-based recommendations for low-risk night work schedules.

Methods: We followed 100 149 night workers (80% women) and 153 882 day workers (78% women), all health care workers in Denmark with day by day payroll information on night shifts from 2007 to 2015. We analysed data with Poisson regression stratified by sex and adjusted for age, calendar year, diabetes, family history of cardiovascular disease, educational level, occupation, indicators for obesity, hypercholesterolaemia, and hypertension.

Results: Female and male night workers worked on average 1.7 and 1.8 night shifts per month for an average duration of less than 4 years. During follow-up, 1198 night and 2128 day workers were hospitalized with first-time coronary heart disease. When compared with day workers, the overall incidence rate ratios for female and male night workers were 1.06 [95% confidence interval (CI): 0.97, 1.17] and 1.22 (95% CI 1.07, 1.39). Highest risks were observed in top exposure categories for several night work characteristics. However, no consistent exposure-response relations by number of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shift and consecutive night shifts were observed among the night workers of either sex.

Conclusions: This study of a population with low exposure to night work does not indicate that reducing extent of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shift and consecutive night shifts would reduce the risk of coronary heart disease.

Keywords: Angina pectoris, myocardial infarction, occupation, follow-up study, shift work.

Key Messages

- Men, but not women, with low-level night work as recorded day by day since 2007, showed a 20% increased risk of coronary heart disease. Highest risks were observed in top exposure categories for several night work characteristics.
- The risk of coronary heart disease did not increase in an exposure-response manner with increasing number of monthly, cumulative or consecutive night shifts, years with rotating night shifts or years with any night shifts, indicating that reducing extent of night work according to these characteristics would not reduce the risk of coronary heart disease in low-exposed populations such as in the current study.

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Introduction

In 2016, the American Nurses' Health Study showed increasing risk of coronary heart disease with increasing years of rotating night shift work.[1] This observation supports a causal association and is the pinnacle of repeated epidemiological evidence of increased risk of cardiovascular diseases following night and other shift work.[2–6] The existing literature of more than 40 studies has relied on self-reported or company employment information on shift work, with few details of night work characteristics.[3–5] This limits evidence-based recommendations for low-risk night work schedules.[6] Such recommendations are needed because night work is widespread and vital societal institutions depend on work outside standard day working hours.[7]

Based on day by day information on starting and ending time of every shift, obtained from payroll data, we analysed coronary heart disease risk following several quantitative night work characteristics, with the aim to contribute to evidence-based recommendations for night work schedules.[8]

Methods

We conducted a register-based nationwide cohort study with follow-up from 2007 to 2015.

Population

From the Danish Working Hour Database of all public hospital workers in Denmark, we identified 261 415 physicians, nurses, auxiliary nurses, janitors, orderlies and other less or higher skilled occupations with at least one work shift of ≥3 h between 1 January 2007 (four hospital regions) or 2008 (one hospital region) and 3 December 2015.[9] We excluded 2738 workers diagnosed with coronary heart disease, as defined later, before start of follow-up and 4646 workers with no data on occupation or educational level.

Coronary heart disease

We defined incident coronary heart disease as the first registration of angina pectoris or myocardial infarction in the National Patient Register that classifies all contacts at all hospitals in Denmark by diagnosis (inpatients 1977–2015, outpatients 1994–2015), supplemented with mortality cases of coronary heart disease identified in the National Causes of Death Register (1970–2015) that includes all deaths occurring in Denmark. We defined angina pectoris by the International Classification of Diseases Revision 10 code (ICD-10) I20 and the ICD-8 code 413, and myocardial infarction by ICD-10 code I21 and ICD-8 code 410.

Night work

We obtained information on night work from the Danish Working Hour Database, which contains individual day by day information on work hours from 1 January 2007 to 31 December 2015. We defined a night shift as a day with ≥3 hours of work between 12:00 AM (midnight) and 5:00 AM.[10] Six time-dependent night work characteristics were constructed at each consecutive day of follow-up: night and day worker, monthly night shifts, cumulative night shifts, years with rotating night shifts, years of any night shift and consecutive night shifts (Box 1). We have previously shown that only 1.1% of men and 1.5% of women of this population were permanent night workers and therefore abstained from including this night work characteristic.[9]

Survey

At the end of follow-up in 2015–16, we e-mailed a questionnaire on smoking, alcohol consumption, height, weight, previous night work and diurnal preference to all currently employed workers ($n = 59\,977$) from three of the five Danish regions.

Statistical analyses

Each health care worker was followed from 1 January 2007 or the first work shift if later, until the day of the first recording of coronary heart disease, death, emigration, disappearance or end of follow-up by 31 December 2015. Associations between night work characteristics (lagged 1 day to secure temporality) and coronary heart disease were analysed with Poisson regression, providing incidence rate ratios (IRR) with 95% confidence intervals (95% CI) with day workers as reference. A priori, we expected no effect modification by sex, but stratified by sex to be able to compare results directly with those of the Vetter *et al.* study that only included women.[1] However, we tested for multiplicative effect modification by interaction terms for sex and the continuous variables of the different night work characteristics among all workers. Analyses were adjusted by age, calendar year, diabetes, obesity, hypercholesterolaemia, hypertension, family history of cardiovascular disease, educational level and

Box 1. Definition of night work characteristics

Six time-dependent night work characteristics were constructed at each consecutive day of follow-up.

i) Night and day worker: a health care worker was defined as a night worker from the first night shift, otherwise as a day worker.
ii) Monthly night shifts: mean number of night shifts per month calculated as the cumulative number of night shifts divided by cumulative months of follow-up (8 categories, rounded up to nearest integer: no night shifts, 1, 2, 3, 4, 5, 6 and >6 night shifts per month).
iii) Cumulative night shifts: number of night shifts (5 categories: no night shifts, 1–5, 6–30, 31–100 and >100 night shifts, category thresholds defined by quartiles of the cumulative number of night shifts, rounded to the nearest integer divisible by 5).
iv) Years with rotating night shifts: number of years with ever ≥3 night shifts per month and at least 1 day and at least 1 evening shift[1] (4 categories: no night shifts, no rotating night shifts, 1 year and ≥2 years, category threshold defined by the median number of years of rotating night shifts). The no rotating night shifts category comprises workers who do not meet the definition, including workers with ≥1 night shift and no day or evening shifts for a given year. The latter category may be regarded as permanent nights.
v) Years of any night shift: number of years with at least 1 night shift (4 categories: no night shifts, <1 year, 1 year and ≥2 years, category threshold defined by the median number of years with at least 1 year with any night shift).
vi) Consecutive night shifts: longest spell of consecutive night shifts (6 categories: no night shifts, never 2 consecutive night shifts, ever 2, ever 3, ever 4 and ever ≥5 consecutive night shifts).

In analyses stratified by age or family history of cardiovascular disease, numbers of monthly night shifts were dichotomized by the median among the night workers (0.91 night shifts) because of fewer person-years (and cases) within each stratum.

occupation. Detailed definitions of these variables are available in the Supplementary material (available as Supplementary data at *IJE* online). All covariates were decided upon a priori based on a review of the literature and the availability of relevant information in the registers.[11,12] The different night work characteristics were moderately correlated and we abstained from mutual adjustment to avoid over-adjustment. All *P*-values were two-sided. All night work and covariate variables were treated as time-varying day by day. We tested for linear trends by levels of night work characteristics, with a continuous variable of consecutive integers among all workers and among night workers only.

Based on questionnaire data from end of follow-up, we tabulated the prevalence of self-reported information on smoking, alcohol consumption, body mass index (BMI), night work before 2007 and diurnal preference, by number of monthly night shifts during follow-up.

In supplementary analyses we repeated analyses stratified by age and family history of cardiovascular disease, and we restricted analysis to person-years provided by workers ever working evenings, because evening work has also been associated with increased risk of coronary heart disease and because evening work was unevenly distributed between day and night workers, as shown later.[2–6] In agreement with the EU General Data Protection Regulations (GDPR), we did not report on groups of less than three persons. All analyses were performed with Stata 17 (StataCorp LLC, College Station, TX).

Results

The study population included 100 149 night workers (20 089 men and 80 060 women) and 153 882 day workers (33 650 men and 120 232 women) aged ≥18 years. Mean age (SD) at start of follow-up was 37.7 years (11.0), 36.5 years (11.0), 39.0 years (13.5) and 38.8 years (12.6), respectively). The workers accumulated a total of 1 638 889 person-years at risk and 10 211 077 night shifts. Male and female night workers worked on average 1.8 and 1.7 night shifts per month, respectively. Male night workers had on average 3.2 years of any night shift and 0.8 years of rotating night shifts. For female night workers, these numbers were 3.6 and 0.9. A total of 1090 male workers were diagnosed with coronary heart disease (667 and 0 cases of angina pectoris and 400 and 23 cases of myocardial infarction identified in the national patient and mortality registers, respectively). A total of 2236 women workers were diagnosed with coronary heart disease (1719 and <15 cases of angina pectoris and 503 and <15 cases of myocardial infarction identified in the national patient and mortality registers, respectively).

A total of 672 men died from other causes, 1022 emigrated and 10 disappeared, according to the Danish Civil Registration Register during follow-up. For women these numbers were 1451, 2127 and 8, respectively.

The distributions of age, calendar year, diabetes, obesity, hypercholesterolaemia and hypertension were roughly similar by number of monthly night shifts, except for a higher prevalence of all medical conditions in the category of >6 monthly night shifts (Table 1). The proportion of physicians and those with more education decreased, and the proportion of nurses, auxiliary nurses and those with less education increased, by number of monthly night shifts. Comparable patterns were seen for men and women. Close to 50% of day workers and nearly all night workers also had evening shifts, except for night workers in the >6 monthly night shifts category.

Male night and day workers showed overall incidence rates of coronary heart disease of 32.3 and 34.2 per 10 000 person-years, respectively. The fully adjusted incidence rate ratio comparing male night with male day workers was 1.22 (95% CI: 1.07, 1.39) (Table 2). Female night and day workers showed overall incidence rate ratios of 16.1 and 17.9 per 10 000 person-years, respectively. The fully adjusted incidence rate ratio was 1.06 (95% CI: 0.97, 1.17).

Among all male workers, there was a 20% increased incidence rate ratio (IRR_{adj} 1.20; 95% CI: 1.02, 1.41) for night workers working 1 night per month compared with day workers. Increased incidence rate ratios were seen for six night shifts per month (IRR_{adj} 2.56; 95% CI: 1.50, 4.37) and for several of the other monthly night work categories. Among male night workers only, six night shifts per month also showed an increased incidence rate ratio (IRR_{adj} 2.19; 95% CI: 1.26, 3.78) but no increase was seen for the other night work categories when compared with the lowest exposure category, and there was no apparent increasing risk with increasing exposure. *P*-values for trend were for all male workers 0.03, and 0.70 for male night workers only.

The incidence rate ratios were 1.71 (95% CI: 1.18, 2.47) and 1.66 (95% CI: 1.14, 2.42) for six night shifts per month among all female workers and female night workers only. No other increases were seen. *P*-values for trend were for all female workers 0.09 and 0.20 for female night workers only. Results for cumulative night shifts, years with rotating night shifts, years with any night shifts, and consecutive night shifts were similar to those seen for monthly night shifts. Few differences were seen between partially adjusted (adjusted for age, calendar year, family history of cardiovascular disease, occupation and educational level, but not diabetes, obesity, hypertension and hypercholesterolaemia) and fully adjusted incidence rate ratios (Supplementary Table S5, available as Supplementary data at *IJE* online; Table 2).

Analyses stratified by age showed increasing risk of coronary heart disease by monthly night shifts for men aged ≥50 years and for women aged 18–39 years, but trend *P*-values were all well above 0.05 when analyses were restricted to night workers only (Supplementary Table S1, available as Supplementary data at *IJE* online).

Among the subset of 34 432 (57% of the eligible) workers who participated in the survey at the end of follow-up, male and female night workers reported lower overall levels of any smoking and alcohol consumption compared with male and female day workers, whereas current BMI levels were comparable (Table 3). However, male and female night workers reported increasing current smoking, current BMI and BMI at age 20, and decreasing alcohol consumption by increasing number of monthly night shifts. Before start of follow-up, 26.9% of male day workers and 50.7% of male night workers reported regular night work which increased with number of monthly night shifts during follow-up. For women day and night workers these numbers were 23.5% and 50.0%, respectively. Night workers, especially women, more often reported being evening persons.

The sensitivity analysis restricted to person-years provided by participants ever working evenings yielded results similar to those obtained from the complete study population (Supplementary Table S2, available as Supplementary data at *IJE* online).

Table 1. Distribution of person-years at risk (%) by number of monthly night shifts among health care workers, Denmark, 2007–15

	Men ($n = 53\,739$)									Women ($n = 200\,292$)								
			Monthly night shifts[a]									Monthly night shifts[a]						
Worker characteristic	Day worker[b]	Night worker[c]	1	2	3	4	5	6	>6	Day worker[b]	Night worker[c]	1	2	3	4	5	6	>6
Person-years	207 846	117 390	61 650	22 170	12 492	6704	3534	1946	8894	791 613	508 360	266 118	90 126	52 990	31 924	18 729	11 617	36 856
Age (years)																		
18–29	20	14	14	15	15	14	15	13	8	18	16	14	20	21	21	19	15	9
30–34	10	17	15	23	21	17	15	15	9	10	17	14	22	22	21	18	16	9
35–39	10	17	15	22	20	16	15	17	13	12	15	15	18	17	17	16	15	12
40–44	10	14	13	13	14	15	15	15	14	12	13	13	12	12	13	14	15	13
45–49	11	12	13	9	10	12	14	13	15	12	12	13	10	10	10	12	13	14
50–54	12	11	12	8	8	11	11	13	15	12	11	12	9	8	8	10	11	14
55–59	11	9	10	6	7	8	8	9	14	11	9	11	7	6	6	7	8	14
60–64	9	6	6	3	4	5	5	5	9	8	5	6	3	3	3	4	5	10
65–69	5	2	3	1	2	2	2	2	3	4	2	2	1	1	1	1	2	4
≥70	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Calendar year of follow-up																		
2007[d]	6	4	2	4	6	9	10	9	8	7	5	3	5	6	8	9	10	10
2008	9	7	6	7	10	12	12	10	10	9	8	7	8	9	11	12	11	11
2009	10	9	8	9	11	11	11	10	11	10	10	9	10	11	11	11	11	11
2010	10	11	10	11	12	11	11	10	11	11	11	11	11	11	12	11	11	11
2011	11	12	12	12	12	11	11	11	11	11	12	12	12	12	11	11	11	11
2012	12	13	13	13	12	11	11	12	12	12	13	13	13	12	11	11	11	11
2013	13	14	14	14	12	11	11	12	12	13	13	14	14	13	12	11	11	11
2014	14	15	16	15	13	11	12	13	13	14	14	15	14	13	12	12	12	11
2015	15	16	18	16	13	12	12	13	13	14	15	16	15	13	12	12	11	11
Diabetes[e]	3.4	3.1	3.1	2.6	3.0	2.5	3.6	2.8	4.6	3.1	3.1	3.0	3.1	3.0	2.7	2.6	3.2	4.3
Obesity[e]	4.7	5.8	5.8	4.8	5.7	5.6	6.1	6.9	8.2	16.7	18.2	18.1	16.5	16.4	17.6	18.3	20.6	26.2
Hypercholesterolaemia and hyperlipidaemia[e]	9.4	7.0	7.3	5.8	5.8	5.8	7.8	7.5	10.0	6.9	5.1	5.7	3.5	3.5	3.4	3.8	4.1	8.8
Essential hypertension[f]	20.2	18.2	19.0	16.5	17.2	15.5	15.9	14.6	22.0	26.4	23.5	24.9	20.9	19.4	20.3	20.0	21.5	30.5
Family history of cardiovascular disease[f]	12.1	13.8	14.2	12.1	13.6	13.4	15.1	15.4	15.6	12.4	13.4	13.3	13.4	13.5	12.8	13.6	14.8	13.9
Educational level																		
≤10 years	14	10	9	7	9	11	15	16	19	11	2	2	1	1	2	2	2	7
11–13 years	33	26	26	18	20	25	31	38	52	37	23	22	17	17	20	22	28	46
>13 years	53	64	65	75	71	64	55	46	29	52	75	76	82	82	79	77	71	47
Occupation																		
Physicians[g]	17	37	34	56	52	41	23	11	2	3	10	10	17	13	8	4	2	0
Nurses and midwives[h]	2	10	8	10	11	14	20	23	13	18	55	51	58	64	67	69	64	40
Auxiliary nurses, janitors and orderlies[i]	35	35	33	27	30	34	41	53	74	29	24	24	18	18	20	23	30	54
Other higher skilled occupations[j]	36	14	20	8	6	8	12	10	10	46	11	16	8	5	5	5	4	6
Other less skilled occupations[k]	10	3	5	0	1	2	5	2	2	4	0	0	0	0	0	0	0	0
Ever evening work[L]	46	96	99	99	99	98	97	96	68	52	96	99	99	98	96	95	92	68

ISCO-08, International Standard Classification of Occupations 2008.

[a] Mean number of night shifts per month at end of study, rounded up to nearest integer.

[b] No night shifts since entry.

[c] Ever ≥1 night shift since entry.

[d] Data available for four of five regions.

[e] A hospital diagnosis or a prescribed medication.

[f] A hospital diagnosis.

[g] ISCO-08 codes 2210, 2211 and 2212.

[h] ISCO-08 codes 2221 and 2222.

[i] ISCO-08 codes 3221, 9112, 9121 and all 5000-series ISCO-08 codes except 5000, 5120, 5153, 5411 and 5419.

[j] Other ISCO-08 codes in series 1000, 2000, 3000 and 4000.

[k] Other ISCO-08 codes in series 5000, 6000, 7000, 8000 and 9000.

[L] Ever ≥1 evening shift since entry.

Table 2. Night work characteristics and risk of coronary heart disease among health care workers, Denmark, 2007–15

	Men (n = 53 739)					Women (n = 200 292)				
Night work characteristic	Cases	Person-years	IR[a]	Day and night workers IRR[b] (95% CI)	Night workers only IRR[b] (95% CI)	Cases	Person-years	IR[a]	Day and night workers IRR[b] (95% CI)	Night workers only IRR[b] (95% CI)
Day worker[c]	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
Night worker[d]	379	117 390	32.3	1.22 (1.07–1.39)		819	508 360	16.1	1.06 (0.97–1.17)	
Monthly night shifts[e]										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
1 night shift/month	206	61 650	33.4	1.20 (1.02–1.41)	1.00	456	266 118	17.1	1.04 (0.93–1.16)	1.00
2 night shifts/month	51	22 170	23.0	1.16 (0.87–1.55)	0.99 (0.72–1.35)	109	90 126	12.1	1.06 (0.87–1.29)	1.02 (0.82–1.26)
3 night shifts/month	39	12 492	31.2	1.45 (1.04–2.01)	1.22 (0.86–1.72)	52	52 990	9.8	0.88 (0.66–1.16)	0.84 (0.63–1.12)
4 night shifts/month	19	6704	28.3	1.17 (0.74–1.86)	0.99 (0.61–1.58)	52	31 924	16.3	1.38 (1.04–1.82)	1.32 (0.99–1.77)
5 night shifts/month	9	3534	25.5	0.93 (0.48–1.81)	0.79 (0.40–1.54)	19	18 729	10.1	0.77 (0.49–1.22)	0.74 (0.47–1.18)
6 night shifts/month	14	1946	71.9	2.56 (1.50–4.37)	2.19 (1.26–3.78)	29	11 617	25.0	1.71 (1.18–2.47)	1.66 (1.14–2.42)
>6 night shifts/month	41	8894	46.1	1.10 (0.80–1.52)	0.95 (0.67–1.36)	102	36 856	27.7	1.12 (0.91–1.37)	1.09 (0.87–1.36)
P for trend				0.03	0.70				0.09	0.20
Cumulative night shifts										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
1–5 night shifts	112	31 939	35.1	1.20 (0.98–1.47)	1.00	239	124 849	19.1	1.09 (0.95–1.25)	1.00
6–30 night shifts	92	32 295	28.5	1.20 (0.96–1.50)	1.02 (0.77–1.35)	208	149 066	14.0	0.99 (0.85–1.15)	0.91 (0.75–1.10)
31–100 night shifts	83	30 359	27.3	1.26 (1.00–1.60)	1.10 (0.82–1.47)	179	130 485	13.7	1.08 (0.92–1.27)	0.99 (0.81–1.20)
>100 night shifts	92	22 797	40.4	1.22 (0.97–1.53)	1.07 (0.81–1.43)	193	103 960	18.6	1.10 (0.94–1.28)	1.02 (0.84–1.24)
P for trend				<0.01	0.54				0.23	0.71
Years with rotating night shifts[f]										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
No rotating night shifts	248	76 222	32.5	1.23 (1.06–1.42)		536	325 505	16.5	1.05 (0.95–1.17)	
1 year with rotating night shifts	69	25 537	27.0	1.10 (0.86–1.42)	1.00	152	106 677	14.2	1.02 (0.86–1.21)	1.00
≥2 years with rotating night shifts	62	15 631	39.7	1.33 (1.02–1.74)	1.18 (0.83–1.68)	131	76 179	17.2	1.17 (0.97–1.41)	1.12 (0.88–1.43)
P for trend				<0.01	0.36				0.14	0.35
Years with any night shifts[g]										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
<1 year with night shifts	37	14 160	26.1	1.42 (1.01–2.01)	1.00	75	58 337	12.9	1.25 (0.97–1.61)	1.00
1 year with night shifts	126	40 181	31.4	1.19 (0.98–1.44)	0.85 (0.55–1.31)	263	160 811	16.4	1.08 (0.94–1.23)	0.77 (0.56–1.07)
≥2 years with night shifts	216	63 048	34.3	1.20 (1.02–1.42)	0.87 (0.56–1.34)	481	289 213	16.6	1.02 (0.91–1.15)	0.73 (0.52–1.01)
P for trend				<0.01	0.80				0.46	0.12
Consecutive night shifts										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
Never 2 consecutive night shifts	156	53 957	28.9	1.21 (1.01–1.45)	1.00	248	151 957	16.3	1.02 (0.89–1.18)	1.00
Ever 2 consecutive night shifts	56	18 905	29.6	1.33 (1.01–1.76)	1.13 (0.83–1.53)	139	78 917	17.6	1.10 (0.92–1.31)	1.07 (0.86–1.32)
Ever 3 consecutive night shifts	38	11 617	32.7	1.13 (0.81–1.58)	0.97 (0.67–1.40)	155	112 359	13.8	0.99 (0.84–1.18)	0.96 (0.78–1.18)
Ever 4 consecutive night shifts	35	9697	36.1	1.32 (0.93–1.86)	1.12 (0.76–1.65)	114	86 624	13.2	1.12 (0.92–1.37)	1.09 (0.86–1.37)
Ever ≥5 consecutive night shifts	94	23 213	40.5	1.18 (0.94–1.47)	1.00 (0.75–1.33)	163	78 503	20.8	1.12 (0.95–1.33)	1.10 (0.89–1.36)
P for trend				0.03	0.97				0.13	0.39

[a] Incidence rate per 10 000 person-years.
[b] Incidence rate ratio, adjusted for age, diabetes, obesity, hypercholesterolaemia, hypertension, family history of cardiovascular disease, calendar year, occupation and educational level.
[c] No night shift since entry.
[d] Ever ≥1 night shift since entry.
[e] Mean number of night shifts per month, rounded up to nearest integer.
[f] Years with ever >3 night shifts per month and ≥1 day shift and ≥1 evening shift. The 'no rotating night shifts' category was not included in the trend analyses.
[g] Years with ≥1 night shifts.

Table 3. Smoking, alcohol consumption, BMI, regular night work before 2007 and diurnal preference among a subset of health care workers, Denmark, 2015–16

Worker characteristic	Day worker[a]	Night worker[b]	*P*	Monthly night shifts[c]							
				1	2	3	4	5	6	>6	*P* for trend
Men (*n* = 5753)	2889	2864		1694	623	256	79	64	28	120	
Smoking[d] (%)											
Any smoking	48.4	45.5	0.02	46.8	34.5	41.4	62.0	67.2	67.9	65.0	0.07
Current smoking	11.6	12.9	0.15	12.3	10.0	12.5	13.9	32.8	14.3	25.0	<0.001
Previous smoking	36.8	32.7	0.001	34.5	24.6	28.9	48.1	34.4	53.6	40.0	0.27
Alcohol consumption (average units per week)[e,f]	6.1	5.7	0.04	6.0	6.1	4.9	5.3	3.8	1.9	4.1	<0.001
BMI, current (mean kg/m^2)[f]	25.9	25.9	0.66	26.0	25.3	25.9	26.4	27.0	28.2	27.5	<0.001
BMI, at age 20 years (mean kg/m^2)[f]	23.1	23.3	0.05	23.3	23.1	22.9	23.4	23.9	23.9	23.8	0.01
Regular night shift work before 2007 (%)[g]	26.9	50.7	<0.001	46.9	52.3	59.4	63.3	51.6	64.3	65.8	<0.001
Diurnal preference (%)											
Definitely morning person	22.0	19.0	0.003	19.9	16.5	20.3	25.3	17.2	10.7	14.2	0.001
Mostly morning person	30.8	27.8	0.008	28.5	28.9	28.1	25.3	20.3	21.4	17.5	<0.001
Mostly evening person	34.3	36.9	0.049	36.7	40.5	34.4	36.7	37.5	32.1	29.2	0.79
Definitely evening person	11.8	15.8	<0.001	14.3	13.6	16.4	12.7	25.0	35.7	38.3	<0.001
Women (*n* = 28 679)	14 240	14 439		8458	2517	1347	778	487	272	580	
Smoking[d] (%)											
Any smoking	43.8	40.9	<0.001	42.0	37.8	37.3	40.0	38.6	42.7	50.5	0.02
Current smoking	10.1	9.8	0.38	9.3	8.8	9.6	9.9	12.1	10.7	20.9	<0.001
Previous smoking	33.6	31.1	<0.001	32.7	29.0	27.7	30.1	26.5	32.0	29.7	<0.001
Alcohol consumption (average units per week)[e,f]	2.8	2.5	<0.001	2.6	2.4	2.2	2.2	2.2	2.3	1.9	<0.001
BMI, current (mean kg/m^2)[f]	24.9	24.8	0.16	24.6	24.8	24.8	25.2	25.4	25.6	26.9	<0.001
BMI, at age 20 years (mean kg/m^2)[f]	21.8	22.1	<0.001	21.9	22.3	22.2	22.5	22.5	22.5	23.0	<0.001
Regular night shift work before 2007 (%)[g]	23.5	50.0	<0.001	48.0	47.5	51.6	51.9	60.8	64.0	68.3	<0.001
Diurnal preference (%)											
Definitely morning person	25.6	19.0	<0.001	20.8	18.0	16.0	16.5	15.2	15.1	12.2	<0.001
Mostly morning person	36.1	32.9	<0.001	33.7	33.5	33.6	35.6	30.4	26.8	19.0	<0.001
Mostly evening person	29.7	35.6	<0.001	34.7	36.7	37.8	33.3	38.0	41.5	36.6	<0.001
Definitely evening person	8.0	11.9	<0.001	10.1	11.2	12.3	13.9	16.0	16.5	31.9	<0.001

BMI, body mass index.
[a] No night shifts since entry.
[b] Ever ≥1 night shift since entry.
[c] Mean number of night shifts per month at end of study, rounded up to nearest integer.
[d] <1% missing.
[e] 1 unit of alcohol is equal to 12 g of alcohol.
[f] 2% missing.
[g] 5% of responses are incomplete and cannot be categorized.

Stratified analyses showed increasing risk of coronary heart disease by monthly night shifts for men with no family history of cardiovascular disease, but trend *P*-values were all above 0.05 when restricted to night workers only (Supplementary Table S3, available as Supplementary data at *IJE* online).

The interaction terms between sex and the night work characteristics showed *P*-values in the range 0.09–0.70. Analyses combining the two sexes showed overall increased risk of coronary heart disease for night workers compared with day workers (IRR 1.11; 95% CI: 1.03, 1.20). Among the night workers only, no obvious trends were seen by any of the night work characteristics (Supplementary Table S4, available as Supplementary data at *IJE* online).

Discussion

This study showed an overall increased incidence rate ratio of coronary heart disease of about 20% for male night workers compared with male day workers. Highest risks were observed in top exposure categories for several night work characteristics. Incidence rate ratios increased steeply to the 20% level without further consistent increase with increasing number of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shifts or consecutive night shifts. No overall increased risk of coronary heart disease was apparent for women.

Comparisons with other studies

This study was inspired by Vetter *et al.*'s report of the Nurses' Health Study showing increasing risk of coronary heart disease in women by increasing years with rotating night shifts, but we did not corroborate their findings.[1] Brown *et al.* and Gu *et al.* also reported increasing risk of coronary heart disease by increasing years with rotating night shifts among women in the Nurses' Health Study population.[13,14] Our study's finding of an overall increased risk of coronary heart disease among male night workers is in line with a long series of earlier studies.[3–5] However, Yadegarfar *et al.* and Yong *et al.*, observed no associations with years of night work in two independent male worker populations.[15,16]

Wang *et al.* observed increasing risk of coronary heart disease with increasing lifetime duration of night shifts for both sexes combined.[17] Torquati *et al.* did not find that sex explained heterogeneity in the relation between shift work and cardiovascular disease across 21 studies included in a meta-regression analysis.[5] Others have found that women are less tolerant to shift work than men, eg, related to more sleep problems and higher levels of fatigue and sleepiness.[18] Taken together, these studies do not provide consistent support for a

sex-specific effect of night work and we observed no statistical interaction by sex.

However, in this study, a night worker was defined by one or more night shifts during follow-up, which is a much wider criterion than in other studies and a cautious comparison of results is warranted. The male and female night workers worked on average 1.8 and 1.7 night shifts per month, respectively, for an average of less than 4 years, and one may thus speculate if this intensity and duration of night work for most workers was below a threshold. In the Vetter *et al.* study, increased risks were seen following 5 or more years of at least three night shifts per month.[1]

The steep increase in incidence rate ratios (eg, from zero to one monthly night shift or from zero to one ranging to five cumulative night shifts) seen among men can hardly be explained by night work per se but points towards other risk factors for coronary heart disease unevenly distributed between male night and day workers. The no increased overall risk of coronary heart disease in women night workers is in contrast with most earlier studies.[3–5]

Limitations and strengths of the study

The lack of information on distant night work, before start of follow-up, is a limitation. The survey data, however, showed increasing prevalence of regular night work before start of follow-up, with increasing number of monthly night shifts during follow-up. On the premise that distant night work is causally related with coronary heart disease, such exposure misclassification could have inflated the response relation with the more recent night work of this study, and cannot explain the null findings.

The high prevalence of night work in the study population before start of follow-up documents that this was not an inception population of newly hired workers. This may have resulted in the inclusion of more night workers less susceptible to night work, which may have deflated real associations and this could at least partly explain the lack of exposure-response patterns.[19] Our population did not allow the definition of an inception population of newly hired workers with a sufficient number of male ($n = 95$) and female ($n = 210$) cases of coronary heart disease for meaningful analysis. However the strongest study so far, the Vetter *et al.* study, showed increased risk of coronary heart disease particularly following recent night work expected to be less influenced by such a selection process.

The population includes few permanent night workers which allowed for no meaningful analyses of risk of coronary heart disease.

A major strength of the study is the detailed day by day information on night work, allowing analyses of quantitative night work characteristics. Since salary depends on working hours, recordings are expected to be complete, precise and valid, given that employers and employees have a common interest in their correctness.[20] Recordings were obtained before diagnoses of coronary heart disease were made and they were therefore unaffected by recall; this may have biased studies relying on self-reports.[3,6] Thus we find that recall bias cannot either explain the negative exposure-response results.

From the payroll registers we had access to, all health care workers of all public hospitals regardless of occupation, workhours and duration of employment since 2007. For this population we had access to all inpatient and outpatient hospital contacts since 1994 as recorded in a national register with high coverage. In Denmark, access to the health care system including hospitals is tax funded, and we thus find that selection bias is an unlikely explanation of our finding of no exposure-response relation.

Cases of coronary heart disease were identified in a national register with 88–93% positive predictive values for first-time diagnoses of angina pectoris and 97% for myocardial infarction, when compared with medical records.[21] Thus, non-differential misclassification of coronary heart disease should not have biased our findings substantially towards the null. The almost complete follow-up of cohort members makes notable social-based selection bias unlikely.

Adjustment was done for known medical risk factors, family history, occupation, educational level, age and calendar year, based on data from national registers with high coverage. Restricting analyses to person-years provided by participants ever working evenings did not affect results. Age was a confounder and was adjusted for in all analyses, and a supplementary analysis stratifying by age did not change findings. Night work has been suggested to increase the risk of type 2 diabetes, obesity, hypertension and hypercholesterolaemia which may be on the path between night work and coronary heart disease.[22–25] Adjusting for these factors may thus have blurred real associations, but including them in the models did not change the partially-adjusted estimates much, and it is unlikely that the fully adjusted analyses are over-adjusted by mediating health factors.

The survey information on smoking, alcohol consumption, BMI and diurnal preference, which was available for a non-random subgroup at the end of follow-up in 2015–16, showed increasing level of smoking and BMI by increasing number of monthly night shifts among the night workers. To the extent that these results are representative of the total study population during follow-up 2007–15, they indicate that our exposure-response analyses have been confounded and overestimate the true values even if the survey data showed decreasing alcohol consumption by increasing number of monthly night shifts. The survey data were, however, obtained from a survivor population and may not be representative and included only 14% of all workers, and for that reason we abstained from including them in adjusted analyses. The survey showed lower overall levels of smoking and alcohol consumption and comparable BMI levels among the male night workers compared with the male day workers, and provided thus no obvious clues to the causes of the increased risk of coronary heart disease seen in male night workers. Day workers never working nights may be fundamentally different from night workers with respect to risk factors that we were unable to document or account for in the analyses and, as such, may not be a suitable reference category. A similar phenomenon was seen for breast cancer in a female subpopulation of the current study[26] and in other occupational cohorts.[27,28] For that reason, the internal trend analyses conducted within night workers only, who are expected to be more homogeneous with respect to unrecognized confounders, are regarded as the most valid.

Conclusion

This study provides evidence for a 20% increased risk of coronary heart disease among men with night shifts, as recorded day by day since 2007. Highest risks were observed in top exposure categories for several night work characteristics. However, no evidence was provided for linear exposure-response relations or other clear association patterns between monthly night shifts, cumulative night shifts, years with rotating night shifts, years of any night shift or consecutive shifts

and coronary heart disease risk among men and women. This indicates that reducing the extent of these night work characteristics would not reduce the risk of coronary heart disease in low-exposed populations such as the current cohort. Results from this low-exposed population may not be applicable for higher-exposed populations.

Ethics approval

According to Danish law, studies based entirely on registry and questionnaire data do not require approval from an ethics review board. The analysis was registered at the repository of the Central Denmark Region (j. no.: 1–16-02–653-18), and data access was approved by the Danish Health Data Authority (707394, FSEID-00004107 and FSEID-00004926).

Data availability

No additional data available. For legal and ethical reasons, individual-level data cannot be shared by the authors and are only accessible to authorized researchers after application to the Danish Health Data Authority.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

J.M.V. and H.A.K. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: J.M.V. and H.A.K. Acquisition, analysis or interpretation of data: J.M.V., H.A.K. and A.D. All authors contributed to interpretation of data. Drafting the manuscript: J.M.V. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: J.M.V. in close collaboration with H.A.K. Administrative, technical or material support: J.M.V., H.A.K. and A.D. Supervision: H.A.K. and A.D.

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Conflict of interest

None declared.

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Night shift characteristics and risk of incident coronary heart disease among health care workers: national cohort study

Supplementary material

Covariates 2

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Covariates

We defined medical risk factors for coronary heart disease from two sources. The Danish National Prescription Register provided all purchases of prescription drugs as defined by the Anatomical Therapeutic Chemical Classification System (ATC codes) 1994-2015.[1] The Danish National Patient Register provided all diagnoses recorded during hospital contacts (ICD-8, 1977-1994 and ICD-10, 1995-2015).[2]

We defined diabetes by ICD-10 codes E10-E14, ICD-8 code 250 or ATC code A10, obesity by ICD-10 code E66, ICD-8 code 277 or ATC code A08, hypercholesterolemia by ICD-10 codes E78.0-E78.2, ICD-8 code 2790 or ATC code C10, and hypertension by ICD-10 code I10, ICD-8 codes 400-401 or ATC codes C02-03 and C07-09. For each medical risk factor, we specified the date when first purchase of prescription drug or diagnosis were recorded and classified participants as affected from this date.

From the Danish Civil Registration Register we obtained information on age that we classified into 10 categories (<30, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69 and ≥70 years), calendar year (9 categories, one for each year 2007-2015).[3]

We defined family history of cardiovascular disease as having a first degree relative with cardiovascular disease recorded in the Danish National Patient Register before age 60 years (ischemic heart disease ICD-10 I20-25, ICD-8 410-414 or ischemic stroke ICD-10 I63, I65-I66, ICD-8 432-435). Participants were classified with a family history from the date cardiovascular disease was first recorded in the first degree relative. Information on first degree relatives (children, siblings, parents) were provided by the Danish Civil Registration Register. A total of 81% of participants had information on both parents. Information was complete for the other covariate variables.

The Danish Working Hour Database provided information on occupation for each health care worker by December 31 each year of employment and classified by the Danish extended version of the International Standard Classification of Occupations version 2008 (ISCO-08). We defined 6 occupational groups: physicians (ISCO-08 codes 2210-2212), nurses and midwifes (ISCO-08 codes 2221-2222), auxiliary nurses, janitors and orderlies (ISCO-08 codes 3221, 9112, 9121 and all 5000-series ISCO-08 codes except 5000, 5120, 5153, 5411 and 5419), other higher skilled occupations (other ISCO-08 codes in series 1000-4000) and other less skilled occupations (other ISCO-08 codes in series 5000-9000). Level of education (3 categories: ≤10 years, 11-13 years and >13 years) was provided by Statistics Denmark. These covariates were decided on a priori.

We defined an evening shift as ≥3 hours of work between 4:00 PM and 10:00 PM and classified participants as having evening work from the first evening shift based on data from The Danish Working Hour Database.

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Supplementary table S1. Night Work Characteristics and Risk of Coronary Heart Disease by Sex and Age among Health Care Workers, Denmark, 2007-2015

	Men (n=53 739)					Women (n=200 292)				
				Crude	Adjusted[a]				Crude	Adjusted[a]
Monthly night shifts[b]	Cases	Person years	IR[c]	IRR[d] (95% CI)	IRR[d] (95% CI)	Cases	Person years	IR[c]	IRR[d] (95% CI)	IRR[d] (95% CI)
18-39 years old										
Monthly night shifts[b]										
None	34	84 176	4.0	1.00	1.00	83	317 128	2.6	1.00	1.00
≤0.91 night shifts per month	15	25 072	6.0	1.48 (0.81-2.72)	1.55 (0.81-2.97)	36	108 199	3.3	1.27 (0.86-1.88)	1.41 (0.91-2.17)
>0.91 night shifts per month	13	29 765	4.4	1.08 (0.57-2.05)	1.20 (0.58-2.49)	57	136 065	4.2	1.60 (1.14-2.24)	1.83 (1.21-2.76)
P value for trend I, all workers				P=.61	P=.50				P<.01	P<.01
P value for trend II, night workers only				P=.41	P=.62				P=.28	P=.21
40-49 years old										
Monthly night shifts[b]										
None	111	44 845	24.8	1.00	1.00	307	192 082	16.0	1.00	1.00
≤0.91 night shifts per month	45	15 595	28.9	1.17 (0.82-1.65)	1.20 (0.84-1.72)	125	65 111	19.2	1.20 (0.98-1.48)	1.25 (0.99-1.56)
>0.91 night shifts per month	48	14 558	33.0	1.33 (0.95-1.87)	1.29 (0.90-1.85)	86	59 420	14.5	0.91 (0.71-1.15)	0.93 (0.72-1.20)
P value for trend I, all workers				P=.09	P=.14				P=.83	P=.91
P value for trend II, night workers only				P=.52	P=.70				P=.04	P=.06
≥50 years old										
Monthly night shifts[b]										
None	566	78 824	71.8	1.00	1.00	1027	282 403	36.4	1.00	1.00
≤0.91 night shifts per month	139	18 434	75.4	1.05 (0.87-1.26)	1.14 (0.94-1.38)	282	81 535	34.6	0.95 (0.83-1.09)	0.97 (0.84-1.11)
>0.91 night shifts per month	119	13 966	85.2	1.19 (0.97-1.45)	1.26 (1.02-1.55)	233	58 029	40.2	1.10 (0.96-1.27)	1.10 (0.95-1.28)
P value for trend I, all workers				P=.10	P=.02				P=.36	P=.34
P value for trend II, night workers only				P=.33	P=.43				P=.09	P=.14
[a] Adjusted for diabetes, obesity, hypercholesterolemia, hypertension, family history of cardiovascular disease, calendar year, job category, and educational level										
[b] Split at the median for exposed workers										
[c] Incidence rate per 10 000 person years										
[d] Incidence rate ratio										

Supplementary table S2. Night Work Characteristics and Risk of Coronary Heart Disease among Health Care Workers ever Working Evening Shifts, Denmark, 2007-2015

	Men (n=35 140)					Women (n=141 029)				
				Age adjusted model	Fully adjusted model[a]				Age adjusted model	Fully adjusted model[a]
Night work characteristic	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)
Day worker[d]	287	94 607	30.3	1.00	1.00	735	411 607	17.9	1.00	1.00
Night worker[e]	360	113 049	31.8	1.19 (1.02-1.39)	1.27 (1.08-1.49)	758	487 127	15.6	1.07 (0.96-1.18)	1.09 (0.97-1.21)
Monthly night shifts[f]										
No night shifts	287	94 607	30.3	1.00	1.00	735	411 607	17.9	1.00	1.00
1 night shifts/month	203	60 784	33.4	1.14 (0.95-1.36)	1.23 (1.03-1.48)	444	262 554	16.9	1.04 (0.93-1.17)	1.06 (0.94-1.20)
2 night shifts/month	50	21 977	22.8	1.12 (0.82-1.51)	1.19 (0.88-1.63)	105	88 739	11.8	1.03 (0.84-1.26)	1.09 (0.88-1.34)
3 night shifts/month	39	12 337	31.6	1.42 (1.01-1.98)	1.54 (1.09-2.16)	51	51 777	9.9	0.88 (0.66-1.18)	0.93 (0.70-1.24)
4 night shifts/month	19	6 586	28.8	1.11 (0.70-1.77)	1.25 (0.78-2.00)	47	30 719	15.3	1.32 (0.98-1.77)	1.36 (1.01-1.83)
5 night shifts/month	9	3 420	26.3	1.00 (0.51-1.93)	1.04 (0.53-2.02)	17	17 778	9.6	0.75 (0.46-1.21)	0.77 (0.48-1.26)
6 night shifts/month	13	1 864	69.7	2.57 (1.48-4.49)	2.61 (1.49-4.57)	25	10 698	23.4	1.63 (1.09-2.43)	1.70 (1.14-2.54)
>6 night shifts/month	27	6 081	44.4	1.27 (0.85-1.88)	1.16 (0.77-1.73)	69	24 863	27.8	1.39 (1.09-1.78)	1.24 (0.96-1.59)
P value for trend I, all workers				P=.02	P=.02				P=.01	P=.03
P value for trend II, night workers only				P=.20	P=.53				P=.02	P=.12
Cumulative night shifts										
No night shifts	287	94 607	30.3	1.00	1.00	735	411 607	17.9	1.00	1.00
1-5 night shifts	108	30 701	35.2	1.14 (0.92-1.42)	1.23 (0.98-1.54)	222	118 921	18.7	1.10 (0.95-1.28)	1.09 (0.93-1.27)
6-30 night shifts	91	31 486	28.9	1.20 (0.95-1.53)	1.27 (1.00-1.62)	198	144 496	13.7	0.99 (0.84-1.16)	1.01 (0.86-1.19)
31-100 night shifts	81	29 715	27.3	1.21 (0.94-1.55)	1.35 (1.04-1.74)	162	126 466	12.8	1.03 (0.87-1.23)	1.08 (0.91-1.29)
>100 night shifts	80	21 147	37.8	1.21 (0.95-1.56)	1.24 (0.96-1.61)	176	97 244	18.1	1.17 (0.99-1.38)	1.19 (1.00-1.41)
P value for trend I, all workers				P=.04	P=.01				P=.16	P=.07
P value for trend II, night workers only				P=.65	P=.58				P=.58	P=.48
Years with rotating night shifts[g]										
No night shifts	287	94 607	30.3	1.00	1.00	735	411 607	17.9	1.00	1.00
No rotating night shifts	229	71 881	31.9	1.17 (0.99-1.40)	1.28 (1.07-1.53)	475	304 272	15.6	1.05 (0.93-1.18)	1.07 (0.95-1.20)
1 year with rotating night shifts	69	25 537	27.0	1.13 (0.87-1.47)	1.15 (0.88-1.50)	152	106 677	14.2	1.04 (0.88-1.24)	1.06 (0.88-1.27)
≥2 years with rotating night shifts	62	15 631	39.7	1.33 (1.01-1.75)	1.37 (1.03-1.82)	131	76 179	17.2	1.19 (0.99-1.44)	1.22 (1.01-1.48)
P value for trend I, all workers				P=.03	P=.02				P=.09	P=.06
P value for trend II, night workers only				P=.50	P=.69				P=.25	P=.34

Supplementary table S2. Night Work Characteristics and Risk of Coronary Heart Disease among Health Care Workers ever Working Evening Shifts, Denmark, 2007-2015 (continued)

				Age adjusted model	Fully adjusted model[a]				Age adjusted model	Fully adjusted model[a]
Night work characteristic	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)
Years with any night shifts[h]										
No night shifts	287	94 607	30.3	1.00	1.00	735	411 607	17.9	1.00	1.00
<1 year with night shifts	35	13 149	26.6	1.35 (0.95-1.92)	1.66 (1.14-2.42)	58	52 161	11.1	1.09 (0.83-1.42)	1.21 (0.90-1.63)
1 year with night shifts	116	38 226	30.3	1.13 (0.91-1.41)	1.22 (0.98-1.52)	239	151 646	15.8	1.11 (0.96-1.29)	1.10 (0.94-1.28)
≥2 years with night shifts	209	61 675	33.9	1.20 (1.00-1.43)	1.24 (1.03-1.49)	461	283 321	16.3	1.05 (0.93-1.17)	1.06 (0.94-1.21)
P value for trend I, all workers				P=.053	P=.02				P=.32	P=.25
P value for trend II, night workers only				P=.85	P=.62				P=.52	P=.10
Consecutive night shifts										
No night shifts	287	94 607	30.3	1.00	1.00	735	411 607	17.9	1.00	1.00
Never 2 consecutive night shifts	153	53 015	28.9	1.09 (0.90-1.33)	1.25 (1.02-1.53)	237	148 454	16.0	0.97 (0.83-1.12)	1.03 (0.88-1.20)
Ever 2 consecutive night shifts	55	18 595	29.6	1.23 (0.92-1.64)	1.37 (1.02-1.84)	131	76 477	17.1	1.12 (0.93-1.35)	1.11 (0.92-1.34)
Ever 3 consecutive night shifts	35	11 271	31.1	1.08 (0.76-1.54)	1.13 (0.79-1.61)	150	109 379	13.7	1.02 (0.86-1.22)	1.04 (0.86-1.24)
Ever 4 consecutive night shifts	35	9 439	37.1	1.45 (1.02-2.06)	1.43 (1.00-2.04)	105	83 802	12.5	1.11 (0.90-1.36)	1.14 (0.92-1.41)
Ever ≥5 consecutive night shifts	82	20 730	39.6	1.33 (1.04-1.70)	1.25 (0.97-1.61)	135	69 015	19.6	1.29 (1.07-1.55)	1.21 (1.00-1.46)
P value for trend I, all workers				P<.01	P=.03				P=.01	P=.04
P value for trend II, night workers only				P=.11	P=.73				P=.02	P=.24
[a] Adjusted for age, diabetes, obesity, hypercholesterolemia, hypertension, family history of cardiovascular disease, calendar year, occupation, and educational level										
[b] Incidence rate per 10 000 person years										
[c] Incidence rate ratio										
[d] No night shift since entry										
[e] Ever ≥1 night shift since entry										
[f] Mean number of night shifts per month rounded up to nearest integer										
[g] Years with ever >3 night shifts per month and ≥1 day shift and ≥1 evening shift										
[h] Years with ≥1 night shifts										

Supplementary table S3. Night Work Characteristics and Risk of Coronary Heart Disease by Sex and Family History of Cardiovascular Disease among Health Care Workers, Denmark, 2007-2015

	Men (n=53 739)					Women (n=200 292)				
				Age adjusted model	Fully adjusted model[a]				Age adjusted model	Fully adjusted model[a]
Monthly night shifts[b]	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)
Employees with no family history of cardiovascular disease										
Monthly night shifts[d]										
None	593	182 603	32.5	1.00	1.00	1207	693 089	17.4	1.00	1.00
≤0.91 night shifts per month	155	50 660	30.6	1.12 (0.93-1.33)	1.20 (1.00-1.44)	371	220 894	16.8	1.06 (0.94-1.19)	1.05 (0.93-1.19)
>0.91 night shifts per month	152	50 492	30.1	1.35 (1.13-1.62)	1.41 (1.17-1.71)	301	219 416	13.7	1.10 (0.97-1.25)	1.07 (0.94-1.22)
P value for trend I, all workers				P<.01	P<.01				P=.10	P=.27
P value for trend II, night workers only				P=.09	P=.18				P=.65	P=.86
Employees with family history of cardiovascular disease[e]										
Monthly night shifts[d]										
None	118	25 243	46.7	1.00	1.00	210	98 524	21.3	1.00	1.00
≤0.91 night shifts per month	44	8 441	52.1	1.16 (0.82-1.64)	1.15 (0.81-1.64)	72	33 952	21.2	0.99 (0.76-1.30)	1.00 (0.76-1.33)
>0.91 night shifts per month	28	7 796	35.9	0.89 (0.59-1.35)	0.72 (0.46-1.10)	75	34 098	22.0	1.19 (0.92-1.56)	1.19 (0.89-1.58)
P value for trend I, all workers				P=.84	P=.26				P=.25	P=.28
P value for trend II, night workers only				P=.31	P=.20				P=.26	P=.28
[a] Adjusted for age, diabetes, obesity, hypercholesterolemia, hypertension, calendar year, occupation, and educational level										
[b] Incidence rate per 10 000 person years										
[c] Incidence rate ratio										
[d] Split at the median for exposed workers										
[e] First degree relatives with cardiovascular disease before age 60										

Supplementary table S4. Night Work Characteristics and Risk of Coronary Heart Disease among Men and Women Health Care Workers combined, Denmark, 2007-2015

	Men and women (n=254 031)				
				Age adjusted model	Fully adjusted model[a]
Night work characteristic	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)
Day worker[d]	2 128	999 459	21.3	1.00	1.00
Night worker[e]	1 198	625 750	19.1	1.11 (1.04-1.20)	1.11 (1.03-1.20)
Monthly night shifts[f]					
No night shifts	2 128	999 459	21.3	1.00	1.00
1 night shifts/month	662	327 768	20.2	1.07 (0.98-1.17)	1.09 (1.00-1.20)
2 night shifts/month	160	112 295	14.2	1.06 (0.90-1.25)	1.09 (0.93-1.29)
3 night shifts/month	91	65 482	13.9	1.04 (0.84-1.28)	1.06 (0.86-1.31)
4 night shifts/month	71	38 628	18.4	1.30 (1.02-1.64)	1.33 (1.05-1.69)
5 night shifts/month	28	22 263	12.6	0.83 (0.57-1.20)	0.83 (0.57-1.20)
6 night shifts/month	43	13 563	31.7	1.94 (1.44-2.63)	1.94 (1.43-2.63)
>6 night shifts/month	143	45 750	31.3	1.29 (1.09-1.53)	1.12 (0.94-1.33)
P value for trend I, all workers				P=<.01	P=<.01
P value for trend II, night workers only				P=<.01	P=.23
Cumulative night shifts					
No night shifts	2 128	999 459	21.3	1.00	1.00
1-5 night shifts	351	156 788	22.4	1.13 (1.01-1.27)	1.13 (1.01-1.27)
6-30 night shifts	300	181 361	16.5	1.05 (0.93-1.18)	1.05 (0.93-1.19)
31-100 night shifts	262	160 844	16.3	1.11 (0.98-1.26)	1.13 (0.99-1.29)
>100 night shifts	285	126 757	22.5	1.17 (1.03-1.32)	1.14 (1.00-1.30)
P value for trend I, all workers				P=<.01	P=.01
P value for trend II, night workers only				P=.63	P=.53
Years with rotating night shifts[g]					
No night shifts	2 128	999 459	21.3	1.00	1.00
No rotating night shifts	784	401 726	19.5	1.10 (1.02-1.20)	1.11 (1.02-1.21)
1 year with rotating night shifts	221	132 214	16.7	1.06 (0.92-1.22)	1.05 (0.91-1.21)
≥2 years with rotating night shifts	193	91 810	21.0	1.23 (1.06-1.43)	1.22 (1.05-1.43)
P value for trend I, all workers				P=<.01	P=<.01
P value for trend II, night workers only				P=.32	P=.33

Supplementary table S4. Night Work Characteristics and Risk of Coronary Heart Disease among Men and Women Health Care Workers combined, Denmark, 2007-2015 (continued)

	Men and women (n=254 031)				
				Age adjusted model	Fully adjusted model[a]
Night work characteristic	Cases	Person years	IR[b]	IRR[c] (95% CI)	IRR[c] (95% CI)
Years with any night shifts[h]					
No night shifts	2 128	999 459	21.3	1.00	1.00
<1 year with night shifts	112	72 497	15.4	1.23 (1.02-1.49)	1.32 (1.08-1.61)
1 year with night shifts	389	200 992	19.4	1.14 (1.02-1.27)	1.11 (1.00-1.24)
≥2 years with night shifts	697	352 261	19.8	1.08 (0.99-1.18)	1.08 (0.99-1.19)
P value for trend I, all workers				P=.02	P=.03
P value for trend II, night workers only				P=.22	P=.15
Consecutive night shifts					
No night shifts	2 128	999 459	21.3	1.00	1.00
Never 2 consecutive night shifts	404	205 915	19.6	1.02 (0.91-1.13)	1.08 (0.97-1.20)
Ever 2 consecutive night shifts	195	97 822	19.9	1.16 (1.01-1.35)	1.17 (1.00-1.35)
Ever 3 consecutive night shifts	193	123 976	15.6	1.04 (0.90-1.21)	1.04 (0.89-1.21)
Ever 4 consecutive night shifts	149	96 321	15.5	1.20 (1.01-1.41)	1.19 (1.00-1.41)
Ever ≥5 consecutive night shifts	257	101 717	25.3	1.27 (1.12-1.45)	1.15 (1.00-1.31)
P value for trend I, all workers				P=<.01	P=<.01
P value for trend II, night workers only				P=<.01	P=.35

[a] Adjusted for sex, age, diabetes, obesity, hypercholesterolemia, hypertension, family history of cardiovascular disease, calendar year, occupation, and educational level

[b] Incidence rate per 10 000 person years

[c] Incidence rate ratio

[d] No night shift since entry

[e] Ever ≥1 night shift since entry

[f] Mean number of night shifts per month rounded up to nearest integer

[g] Years with ever >3 night shifts per month and ≥1 day shift and ≥1 evening shift

[h] Years with ≥1 night shifts

Supplementary Table S5. Night Work Characteristics and Risk of Coronary Heart Disease among Health Care Workers, Age and Partially Adjusted Results, Denmark, 2007-2015

	Men (n=53 739)				Women (n=200 292)			
	Day- and night workers		Night workers only		Day- and night workers		Night workers only	
	Age adjusted model	Partially adjusted model[a]	Age adjusted model	Partially adjusted model[a]	Age adjusted model	Partially adjusted model[a]	Age adjusted model	Partially adjusted model[a]
Night work characteristic	IRR[c] (95% CI)	IRR[c] (95% CI)	IRR[c] (95% CI)	IRR[c] (95% CI)	IRR[c] (95% CI)	IRR[c] (95% CI)	IRR[c] (95% CI)	IRR[c] (95% CI)
Day worker[d]	1.00	1.00			1.00	1.00		
Night worker[e]	1.19 (1.05-1.35)	1.18 (1.03-1.34)			1.08 (0.99-1.18)	1.05 (0.95-1.15)		
Monthly night shifts[f]								
No night shifts	1.00	1.00			1.00	1.00		
1 night shifts/month	1.14 (0.98-1.34)	1.15 (0.98-1.35)	1.00	1.00	1.04 (0.94-1.16)	1.03 (0.92-1.15)	1.00	1.00
2 night shifts/month	1.13 (0.84-1.50)	1.16 (0.87-1.55)	0.99 (0.73-1.35)	1.02 (0.75-1.40)	1.03 (0.85-1.26)	1.03 (0.84-1.25)	0.98 (0.79-1.21)	0.99 (0.80-1.23)
3 night shifts/month	1.40 (1.01-1.94)	1.40 (1.01-1.94)	1.23 (0.87-1.74)	1.22 (0.86-1.72)	0.87 (0.66-1.14)	0.85 (0.64-1.12)	0.82 (0.62-1.09)	0.82 (0.62-1.10)
4 night shifts/month	1.10 (0.69-1.73)	1.08 (0.68-1.71)	0.96 (0.60-1.53)	0.94 (0.58-1.50)	1.38 (1.05-1.82)	1.34 (1.01-1.77)	1.31 (0.98-1.75)	1.30 (0.97-1.74)
5 night shifts/month	0.95 (0.49-1.84)	0.90 (0.47-1.74)	0.84 (0.43-1.63)	0.78 (0.40-1.53)	0.77 (0.49-1.22)	0.74 (0.47-1.16)	0.74 (0.47-1.17)	0.72 (0.45-1.14)
6 night shifts/month	2.64 (1.56-4.49)	2.46 (1.44-4.19)	2.30 (1.34-3.96)	2.18 (1.26-3.77)	1.71 (1.19-2.48)	1.59 (1.10-2.30)	1.64 (1.12-2.38)	1.55 (1.07-2.26)
>6 night shifts/month	1.25 (0.91-1.72)	1.10 (0.80-1.53)	1.09 (0.78-1.53)	0.98 (0.69-1.40)	1.32 (1.08-1.61)	1.15 (0.94-1.42)	1.27 (1.02-1.58)	1.14 (0.91-1.42)
P value for trend	P<.01	P=.055	P=.25	P=.64	P<.01	P=.09	P=.01	P=.14
Cumulative night shifts								
No night shifts	1.00	1.00			1.00	1.00		
1-5 night shifts	1.15 (0.94-1.40)	1.13 (0.93-1.39)	1.00	1.00	1.13 (0.99-1.30)	1.10 (0.96-1.27)	1.00	1.00
6-30 night shifts	1.18 (0.95-1.47)	1.20 (0.96-1.50)	1.03 (0.78-1.36)	1.08 (0.82-1.44)	1.00 (0.86-1.15)	0.97 (0.84-1.13)	0.88 (0.73-1.05)	0.89 (0.73-1.07)
31-100 night shifts	1.20 (0.95-1.51)	1.23 (0.97-1.56)	1.05 (0.79-1.40)	1.14 (0.84-1.53)	1.07 (0.92-1.25)	1.05 (0.89-1.24)	0.94 (0.77-1.14)	0.95 (0.78-1.16)
>100 night shifts	1.24 (1.00-1.55)	1.17 (0.93-1.46)	1.09 (0.82-1.43)	1.08 (0.81-1.43)	1.13 (0.97-1.31)	1.06 (0.91-1.24)	1.00 (0.83-1.21)	0.97 (0.80-1.18)
P value for trend	P<.01	P=.03	P=.55	P=.56	P=.11	P=.48	P=.90	P=.90
Years with rotating night shifts[g]								
No night shifts	1.00	1.00			1.00	1.00		
No rotating night shifts	1.18 (1.02-1.36)	1.17 (1.01-1.36)			1.07 (0.97-1.19)	1.05 (0.94-1.16)		
1 year with rotating night shifts	1.13 (0.88-1.45)	1.12 (0.87-1.44)	1.00	1.00	1.03 (0.87-1.22)	1.00 (0.84-1.19)	1.00	1.00
≥2 years with rotating night shifts	1.33 (1.03-1.73)	1.27 (0.97-1.66)	1.16 (0.82-1.64)	1.09 (0.77-1.55)	1.18 (0.99-1.41)	1.12 (0.93-1.35)	1.14 (0.91-1.44)	1.10 (0.86-1.40)
P value for trend	P<.01	P=.02	P=.39	P=.64	P=.06	P=.29	P=.26	P=.46

Supplementary table S5. Night Work Characteristics and Risk of Coronary Heart Disease among Health Care Workers, Age and Partially Adjusted Results, Denmark, 2007-2015 (continued)

	Men (n=53 739)				Women (n=200 292)			
	Day- and night workers		Night workers only		Day- and night workers		Night workers only	
	Age adjusted model	Partially adjusted model[a]	Age adjusted model	Partially adjusted model[a]	Age adjusted model	Partially adjusted model[a]	Age adjusted model	Partially adjusted model[a]
Years with any night shifts[h]								
No night shifts	1.00	1.00			1.00	1.00		
<1 year with night shifts	1.28 (0.92-1.78)	1.38 (0.98-1.94)	1.00	1.00	1.21 (0.95-1.52)	1.25 (0.97-1.61)	1.00	1.00
1 year with night shifts	1.16 (0.96-1.41)	1.15 (0.95-1.40)	0.91 (0.63-1.31)	0.86 (0.55-1.33)	1.13 (0.99-1.29)	1.09 (0.95-1.25)	0.94 (0.73-1.22)	0.78 (0.56-1.08)
≥2 years with night shifts	1.19 (1.02-1.39)	1.16 (0.99-1.36)	0.93 (0.66-1.32)	0.87 (0.56-1.35)	1.04 (0.94-1.15)	0.99 (0.89-1.11)	0.87 (0.68-1.11)	0.70 (0.50-0.98)
P value for trend	P=.01	P=.04	P=.88	P=.76	P=.22	P=.74	P=.17	P=.04
Consecutive night shifts								
No night shifts	1.00	1.00			1.00	1.00		
Never 2 consecutive night shifts	1.10 (0.92-1.31)	1.15 (0.96-1.37)	1.00	1.00	0.98 (0.86-1.12)	1.02 (0.88-1.17)	1.00	1.00
Ever 2 consecutive night shifts	1.23 (0.93-1.62)	1.28 (0.97-1.68)	1.12 (0.83-1.52)	1.14 (0.84-1.55)	1.14 (0.96-1.36)	1.10 (0.92-1.32)	1.16 (0.94-1.43)	1.08 (0.87-1.33)
Ever 3 consecutive night shifts	1.12 (0.81-1.56)	1.10 (0.79-1.54)	1.02 (0.72-1.46)	1.00 (0.69-1.45)	1.01 (0.86-1.20)	0.96 (0.81-1.14)	1.03 (0.84-1.26)	0.94 (0.76-1.16)
Ever 4 consecutive night shifts	1.39 (0.99-1.96)	1.31 (0.93-1.86)	1.26 (0.88-1.82)	1.19 (0.81-1.75)	1.13 (0.93-1.37)	1.08 (0.88-1.31)	1.14 (0.91-1.43)	1.05 (0.84-1.32)
Ever ≥5 consecutive night shifts	1.31 (1.05-1.62)	1.16 (0.93-1.45)	1.18 (0.91-1.53)	1.04 (0.78-1.39)	1.26 (1.07-1.48)	1.13 (0.95-1.33)	1.29 (1.06-1.57)	1.11 (0.90-1.37)
P value for trend	P<.01	P=.047	P=.16	P=.72	P<.01	P=.20	P=.03	P=.43

[a] Adjusted for age, family history of cardiovascular disease, calendar year, occupation, and educational level

[b] Incidence rate per 10 000 person years

[c] Incidence rate ratio

[d] No night shift since entry

[e] Ever ≥1 night shift since entry

[f] Mean number of night shifts per month rounded up to nearest integer

[g] Years with ever >3 night shifts per month and ≥1 day shift and ≥1 evening shift. The No rotating night shifts category was not included in the trend analyses

[h] Years with ≥1 night shifts

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This validation study shows that female breast cancer patients had slightly better recall of previous ever-night shift work than controls without breast cancer. Both breast cancer patients and controls recalled previous never-night shift work with low specificity. The net effect of this misclassification is a small over-estimation of the relative breast cancer risk due to night shift work.

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Key terms: breast cancer; case; control; gold standard; misclassification; night shift; night work; patient; self-report; shift work; validation study; validity; women

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Validity of self-reported night shift work among women with and without breast cancer

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Objectives This study aimed to estimate the validity of self-reported information on ever-night shift work among women with and without breast cancer and illustrate the consequences for breast cancer risk estimates.

Methods During 2015–2016, 225 women diagnosed with breast cancer and 1800 matched controls without breast cancer employed within the Danish hospital regions during 2007–2016 participated in a questionnaire-based survey. Their reported night shift work status was linked with objective payroll register day-by-day working hour data from the Danish Working Hour Database and the Danish Cancer Registry. For the breast cancer patients and their matched controls, we estimated sensitivity and specificity for ever-working night shifts using the payroll data as the gold standard. We also used quantitative bias analysis to estimate the impact on relative risk estimates for a hypothetical population.

Results For breast cancer patients, we observed a sensitivity of ever-night shifts of 86.2% and a specificity of never-night shifts of 82.6%. For controls, the sensitivity was 80.6% and the specificity 83.7%. Odds ratio for breast cancer in a hypothetical population decreased from 1.12 [95% confidence interval (CI) 1.03–1.21] to 1.05 (95% CI 0.95–1.16) when corrected by the sensitivity and specificity estimates.

Conclusion This study shows that female breast cancer patients had slightly better recall of previous night shift work than controls. Additionally, both breast cancer patients and controls recalled previous never-night shift work with low specificity. The net effect of this misclassification is a small over-estimation of the relative breast cancer risk due to night shift work.

Key terms case; control; gold standard; misclassification; night work; patient; validation study.

In 2007, the International Agency for Research on Cancer (IARC) concluded that shift work involving circadian disruption and, in 2020, that night shift work are probably carcinogenic to humans (Group 2A) (1, 2). The latter conclusion was based on sufficient evidence in experimental animals for the carcinogenicity of alteration in the light–dark schedule, strong evidence in experimental systems that alteration in the light–dark schedule exhibits key characteristics of carcinogenesis, and limited evidence in humans for the carcinogenicity of night shift work (2). The strongest epidemiological evidence was, according to the IARC evaluation, seen in case–control studies of breast cancer (2). The largest case–control study, a pooled analysis of five case–control studies by Cordina-Duverger et al (3), reported an overall odds ratio (OR) of 1.12 [95% confidence interval

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(CI) 1.00–1.25] for breast cancer among women who ever worked night shifts. The Nurses' Health Study, a large prospective follow-up study, showed a two-fold – but no overall – increased risk of breast cancer among participants who were young at the time of enrollment and had worked rotating night shifts for ≥20 years or more (4). Most studies included in the IARC evaluation of breast cancer relied on self-reported data on night shift work through face-to-face interviews (5–7), in-person questionnaires (8–10), self-administered questionnaires (4, 11) or a combination thereof (3).

Differential exposure misclassification is a potential challenge in case–control studies relying on recall of previous exposures as cases may tend to identify possible reasons for their disease contrary to healthy controls (12). Non-differential misclassification of exposure may bias results of case–control as well as follow-up studies (13, 14). Therefore, validation studies and quantitative bias analysis are important to understand and evaluate the magnitude of such biases (15). We compared, for the first time, the validity of self-reported night shift work among women with and without breast cancer and assessed the impact on breast cancer risk estimates.

Methods

Population

The Danish Working Hour Database (DWHD) provided information on every female employee (N=206 894) from every Danish public hospital in all five regions with information on day-by-day working hours from payrolls from 1 January 2007 (four regions) and 1 January 2008 (one region), or the first day of employment if later, until 31 December 2015, or last date of employment if earlier (16). In 2015–2016, 48 909 currently employed female workers in three of the five regions were invited to participate in an e-mail-based survey on working hours and related topics (17). A total of 29 497 employees (60.7% among breast cancer patients and 60.3% among potential controls) responded and 27 438 (93%) provided complete information on night shift work and alcohol consumption for further analyses. Most workers also reported height and weight used to calculate body mass index and smoking status.

Breast cancer patients and controls

Data on breast cancer was obtained from the Danish Cancer Registry, which keeps records on all cancers diagnosed in Denmark since 1943. A total of 225 women participants were diagnosed with first time breast cancer (ICD-10: C50) after their first year of employment (as recorded in DWHD, ie, 2008/2009) and before the date of participation in the survey, and were included in the analyses. The first time restriction was because at least one previous calendar year with employment information was needed for night shift work status classification (as defined later). We denote the calendar year when breast cancer was diagnosed as the "index year".

For each breast cancer patient, we randomly selected eight matched controls without breast cancer (the maximum number available given the matching criteria) with replacement among the potential controls. A participant was a potential control for a specific breast cancer patient if she was not diagnosed with breast cancer, had the same age and reported the same alcohol consumption (<3 versus ≥3 units/week) as the breast cancer patient at the time of the survey. Furthermore, she should have the same night shift work status (ever- versus never-night shift work as defined below) as recorded in DWHD prior to the index year to have a balanced distribution of night shift work among patients and controls. In total 1800 controls (1717 unique individuals) were selected.

Night shift work

A night shift was defined as ≥3 hours of work between 24:00 and 06:00 hours. Night shift work was classified as ever-night shift work that was defined as ever≥1 month with ≥3 night shifts from first recorded year of employment until and including the year before the index year, else as never-night shift work. Our definition was comparable with that used in the Nurses' Health Study except that it did not require day- or evening shifts in addition to the night shifts within a month (4). We decided on this definition because the Nurses' Health Study has provided several highly influential results on health effects of night shift work (4, 18, 19). According to the DWHD data, 94.8% of cases classified with ever-night shift work in the current study population had rotating night shift work as defined in the Nurses' Health Study. For controls, the figure was 90.0%. The definition of night shift work applied equally to survey and payroll register data. The brief survey questionnaire is shown in figure 1.

DWHD provided information on occupation. Survey data, breast cancer diagnosis, and DWHD data were linked at individual level by the unique personal identification number that all residents of Denmark are applied.

According to Danish law, studies based entirely on registry and questionnaire data do not require approval from an ethics review board. All questionnaire participants gave informed consent. The analysis was registered at the repository of the Central Denmark Region (j. no: 1–16-02–653-18), and the Danish Health Data Authority approved data access (707394, FSEID-00004107 and FSEID-00004926).

Figure 1. 2015-2016 questionnaire on previous night shift work and lifestyle

Have you ever worked at night regularly at least 3 nights per month? 'Night' meaning at least 3 hours between 24:00-6:00.

(1) ☐ Yes
(2) ☐ No
(3) ☐ Don't know

When did you start working at night regularly? ____
When did you stop working at night regularly?
(1) ☐ I still work at night
(2) ☐ I have stopped working at night
Which year did you stop working at night? ____
How tall are you? ____
How much do you weigh currently? ____
How much did you weigh when you were 20 years old? ____
Do you smoke?
(1) ☐ Yes
(2) ☐ No, but I did smoke previously
(3) ☐ No, I have never smoked

How many units of alcohol do you drink on average per week? ____
One unit is equal to: 1 ordinary beer, 1 glass of wine, 1 glass of liquor (4 cl)

Are you a morning person or an evening person?
(1) ☐ Definitely morning person
(2) ☐ More morning person than evening person
(3) ☐ More evening person than morning person
(4) ☐ Definitely evening person

Statistical methods

We estimated sensitivity (probability of true ever-night shift work) and specificity (probability of true never-night shift work) of self-reported compared with register-based night shift work, which we considered the gold standard. We computed 95% CI using 100 bootstrap datasets, each based on a sample with replacement of the 225 breast cancer patients and their matched controls. We calculated the difference in sensitivity and specificity between breast cancer patients and controls.

We furthermore conducted a quantitative bias analysis for a hypothetical population comparing the observed risk estimate for breast cancer following ever-night shift work to the risk estimates obtained after correcting the night shift work misclassification by the sensitivity and specificity estimates (20). The hypothetical population included 6000 breast cancer cases and 6000 controls, had an exposure prevalence among the controls as in our study population and a risk estimate for breast cancer following night shift work as in the Cordina-Duverger et al (3) pooled study which included 6093 breast cancer cases and 6933 breast cancer free controls. Analyses were conducted using Stata version 17 (StataCorp, College Station, TX, USA) and the Excel spreadsheet of Lash, Fox and Fink (20).

Results

Participants with ever-night shift work were younger than those with never-night shift work, consumed less alcohol, were more often never smokers and primarily employed as physicians or nurses (table 1). Only 58 (26%) breast cancer patients were identified as having worked night shifts in accordance with the definition in the DWHD (table 2). The same proportion (26%) was seen in controls because of the matching.

Of 58 breast cancer patients, 50 reported ever-night shift work in agreement with our gold standard register data, corresponding with a sensitivity of 86.2% (95% CI 77.3%–95.1%) (table 2). The corresponding sensitivity for controls was 80.6% (95% CI 76.9%–84.3%). The specificity was 82.6% (95% CI 76.4%–88.8%) for breast cancer patients and 83.7% (95% CI 81.7%–85.7%) for controls. The differences in sensitivity and specificity were 5.6% (95% CI -4.8%–16.0%) and -1.1% (95% CI -7.4%–5.2%) when comparing breast cancer patients with controls.

Table 1. Characteristics of breast cancer patients and matched controls among Healthcare workers, Denmark 2007–2016.

Characteristics	Breast cancer patients		Controls	
	Never-night shift work [a]	Ever-night shift work [a]	Never-night shift work [a]	Ever-night shift work [a]
	N=167	N=58	N=1336	N=464
	N (%)	N (%)	N (%)	N (%)
Age (years)				
<50	40 (24.0)	21 (36.2)	320 (24.0)	168 (36.2)
50–54	44 (26.3)	17 (29.3)	352 (26.3)	136 (29.3)
55–59	40 (24.0)	14 (24.1)	320 (24.0)	112 (24.1)
≥60	43 (25.7)	6 (10.3)	344 (25.7)	48 (10.3)
Alcohol units per week on average				
<3	86 (51.5)	36 (62.1)	688 (51.5)	288 (62.1)
≥3	81 (48.5)	22 (37.9)	648 (48.5)	176 (37.9)
Body mass index (kg/m^2)				
<25 (normal weight)	96 (57.5)	31 (54.4)	793 (59.9)	268 (58.1)
25–<30 (overweight)	45 (26.9)	21 (36.8)	365 (27.6)	128 (27.8)
≥30 (obese)	26 (15.6)	5 (8.8)	165 (12.5)	65 (14.1)
Smoking				
Current	13 (7.8)	4 (6.9)	126 (9.5)	45 (9.8)
Previous	85 (51.2)	22 (37.9)	535 (40.2)	170 (37.0)
Never	68 (41.0)	32 (55.2)	669 (50.3)	245 (53.3)
Occupation				
Physicians	6 (3.6)	9 (15.5)	62 (4.7)	41 (8.8)
Nurses and midwifes	54 (32.3)	38 (65.5)	486 (36.6)	287 (61.9)
Auxiliary nurses, janitors and orderlies	28 (16.8)	8 (13.8)	175 (13.2)	94 (20.3)
Other	79 (47.3)	3 (5.2)	606 (45.6)	42 (9.1)
Index year [b]				
2008–2012	78 (46.7)	28 (48.3)	624 (46.7)	224 (48.3)
2013–2016	89 (53.3)	30 (51.7)	712 (53.3)	240 (51.7)

[a] Never-night shift work and ever-night shift work defined by payroll data.
[b] Calendar year the breast cancer patient was diagnosed with breast cancer, split in two groups by the median.

Table 2. Sensitivity and specificity of self-reported versus payroll register night shift work for women breast cancer patients and their matched controls, Denmark, 2007–2016. [CI=confidence intervals, in this case based on 100 bootstraps.]

	Breast cancer patients				Controls			
	Payroll register				Payroll register			
	Ever-night shift work		Never-night shift work		Ever-night shift work		Never-night shift work	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Self-reported								
Ever-night shift work	50	86.2 (77.3–95.1)	29	17.4 (11.2–23.6)	374	80.6 (76.9–84.3)	218	16.3 (14.3–18.3)
Never-night shift work	8	13.8 (4.9–22.7)	138	82.6 (76.4–88.8)	90	19.4 (15.7–23.1)	1118	83.7 (81.7–85.7)

Table 3. Observed and corrected odds ratios of night shift work and breast cancer from quantitative bias analysis of a hypothetical population. [CI=confidence intervals.]

	Observed				Corrected [a]			
	Cases	Controls	Odds ratio	95% CI	Cases	Controls	Odds ratio	95% CI
Ever-night shift work	1695	1560			946	905		
Never-night shift work	4305	4440	1.12	1.03–1.21	5054	5095	1.05	0.95–1.16
Total	6000	6000			6000	6000		

[a] Corrected numbers calculated from sensitivity and specificity estimates of night shift work obtained among breast cancer patients and matched controls employed within 3 of 5 Danish hospital regions, 2007–2015, Denmark, using Excel spreadsheet of Lash, Fox and Fink (20).

The quantitative bias analysis of the hypothetical population with an exposure prevalence of 26% among the controls and an odds ratio of 1.12 showed a corrected OR of 1.05 (95% CI 0.95–1.16) (table 3).

Discussion

This study of primarily hospital employees observed a slightly higher sensitivity of self-reported ever-night shift work among breast cancer patients (86.2%) than among matched controls without breast cancer (80.6%) when compared with objective payroll information on night shift work. This study also observed low specificity among breast cancer patients and controls, showing that both groups had difficulties classifying themselves correctly as never-night shift workers in the survey.

Our suggestive finding of better recall of previous night shift work among breast cancer patients compared to their matched controls is a concern because this pattern of differential misclassification tends to inflate risk ratio estimates (12, 14). On the other hand, low specificity of exposure classification tends to deflate risk ratio estimates. The quantitative bias analysis of the hypothetical population showed that the net effect of such differential and non-differential misclassification produced a corrected risk ratio estimate that was slightly lower (OR=1.05) than the naive estimate (OR=1.12). This finding underpins the importance of considering both types of exposure misclassification when interpreting results of epidemiological studies and the strength of quantitative bias analysis when a gold standard is available (20). It has to be emphasized that our results relate to the current (or a similar) study population and may not be generalizable to other study populations with a different prevalence of night shift work.

Comparison with other studies

Härmä et al (21) observed a 96% sensitivity and a 92% specificity of self-reported "shift work with night shifts" among hospital employees when compared with individual-level payroll records. The higher sensitivity and specificity compared with ours is likely due to a wider formulation of the questions used in the survey (and consequently the definitions of the payroll data). They defined night shift work by a question stating "*What is your usual work schedule?*", with "*Shift work with night shifts*" being one of five response options. We used the following question: "*Have you ever worked at night regularly at least 3 nights per month? Nights meaning at least 3 hours between 24:00–06:00*". The questions used in the Härmä study may have allowed for a more accurate classification of night shift work compared to our questions, which were much narrower. Härmä did not consider validity related to breast cancer status. Lizama et al (22) observed that breast cancer patients more often than controls believed that shift work increase the risk of breast cancer, but they did no formal evaluation of misclassification. We are not aware of other studies validating self-reported night shift work.

Quantitative bias analysis can offer valuable insight into the impact of exposure misclassification; however, there are few examples in the occupational literature. Notably, Deltour (23) showed lower risk estimates of acoustic neuroma after correcting self-reported occupational noise exposure using quantitative bias analysis.

Biased recall of other occupational exposures have been assessed without conducting a formal bias analysis of the net-effect of differential and non-differential recall (23–26), leaving the field unsure of the impact of the misclassification on the reported risk ratio estimate.

Limitations and strengths

Our study population had to survive for up to eight years (median three) from the index year and remain employed within the five hospital regions to participate. Even if 91% of breast cancer patients in the total DWHD population returned to work within half a year, this may have affected our validity estimates compared with estimates based on self-reports obtained with a short lag (the case for most case–control studies). It is unclear if this lag will affect breast cancer patients and controls differently. Further, the participation proportion in our survey was only about 60% and might be skewed compared to the entire population.

The availability of payroll data for only recent night work (2007–2015) and only covering employment within the five hospital regions are also limitations. The skewed distribution of physicians and nurses between breast cancer patients and controls could be a problem if they have better (or worse) memory of night shift work than the other occupations. Unfortunately, the limited number of breast cancer patients did not allow matching on occupation.

The small number of breast cancer patients with ever-night shift work resulted in uncertain estimates of sensitivity that can only be solved with a larger study population, a broader night shift work definition, or a higher prevalence of night shift work.

The main strengths of this study were the concurrent availability of self-reported and detailed register-based payroll information on working hours, the latter collected prior to breast cancer diagnosis and a nationwide and virtually complete cancer registry, making it possible to compare the sensitivity and specificity by breast cancer status.

In conclusion, this study of Danish female hospital employees shows that breast cancer patients slightly better recall previous ever-night shift work compared to controls while both breast cancer patients and controls recall previous never-night shift work with low specificity. The net effect of this misclassification is expected to be a small over-estimation of the relative risk of breast cancer following night shift work for a study conducted in a similar population and using a similar, singular, night shift work survey question.

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Conflict of interest

The authors declare no conflicts of interest.

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