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Night and shift work and incidence of cerebrovascular disease – a prospective cohort study of healthcare employees in Stockholm

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ABSTRACT (ENGLISH)

Objective This study aimed to investigate the effects of various aspects of night and shift work regarding incident cerebrovascular disease (CeVD). Methods The cohort included 26 667 women and 3793 men (nurses and nursing assistants) who were employed for at least one year 2008-2016 in Region Stockholm, Sweden. Information about the cohort and working hours were obtained from a computerized employee-register and diagnoses were retrieved from national and regional registers. We used discrete time proportional hazard models to assess the risk of CeVD (2009-2017), in relation to work hour characteristics, adjusting for sex, age, country of birth, education and profession. Results We observed an excess risk of CeVD (N=223) among employees who, during the preceding year, worked night shifts >30 times [hazard ratio (HR) 1.44, 95% confidence interval (CI) 1.04-1.99] or >3 consecutive night shifts >15 times (HR 1.69, 95% CI 1.18-2.42) or with >30 quick returns (<28 hours) from night shifts (HR 1.52, 95% CI 1.10-2.10) compared to those who did not work nights. We also observed an excess risk among employees with a long duration (>5 years) of exposure to night shift work (HR 1.87, 95% CI 1.27-2.77), all supported by a dose-response pattern. Conclusions Our results show that the risk of CeVD among nurses and nursing assistants is associated with night shift work. The number of years with night shift work, the frequency of night shifts per year, the frequency of consecutive night shifts, and short recovery after night shifts influenced the risk. Work schedules aiming at minimizing these aspects of night shift work may reduce the risk.

FULL TEXT

Headnote

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Objective This study aimed to investigate the effects of various aspects of night and shift work regarding incident cerebrovascular disease (CeVD).

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Results We observed an excess risk of CeVD (N=223) among employees who, during the preceding year, worked night shifts >30 times [hazard ratio (HR) 1.44, 95% confidence interval (CI) 1.04-1.99] or >3 consecutive night shifts >15 times (HR 1.69, 95% CI 1.18-2.42) or with >30 quick returns (<28 hours) from night shifts (HR 1.52, 95% CI 1.10-2.10) compared to those who did not work nights. We also observed an excess risk among employees with a long duration (>5 years) of exposure to night shift work (HR 1.87, 95% CI 1.27-2.77), all supported by a dose-

response pattern.
Conclusions Our results show that the risk of CeVD among nurses and nursing assistants is associated with night shift work. The number of years with night shift work, the frequency of night shifts per year, the frequency of consecutive night shifts, and short recovery after night shifts influenced the risk. Work schedules aiming at minimizing these aspects of night shift work may reduce the risk.
Key terms night shift; shift worker; stroke; occupational exposure; occupational health.
Cerebrovascular disease (CeVD) includes diseases that affect the cerebral blood vessels and blood supply and are mainly related to occlusion or vascular bleeding. The most common CeVD is ischemic stroke (1). Stroke is one of the leading causes of death and disability worldwide. Although the age-standardized stroke mortality rates have decreased globally over time, the absolute number of stroke occurrences and deaths have increased (2, 3).
The underlying mechanisms for CeVD may vary depending on the disease and involve an interaction of vascular risk factors, environmental and genetic factors. Many of the risk factors associated with lifestyle and environment are modifiable, such as hypertension, tobacco use, hyperlipidemia, diabetes, unhealthy dietary patterns, obesity and physical inactivity (4).
There is accumulating evidence that working time patterns like shift work, night work and long working hours may increase the risk of CeVD (5-10). Therefore, efforts to develop and modify existing work schedules for those who need to work non-standard working hours are important parts for risk management. Potential mechanisms linking night and shift work or long working hours to CeVD include disruption of the circadian rhythm, sleep deprivation, insufficient recovery, hor monal effects, stress mechanisms, inflammation, vascular effects, and metabolic disturbances (7, 9, 11-16). Several different aspects of night and shift work may possibly be important components influencing the risk of CeVD, such as the frequency of night shifts or the frequency of consecutive night shifts, related to circadian disruption, insufficient recovery and accumulated sleep debt (15). Another aspect is quick returns from work shifts, leading to sleep deprivation and an increased level of perceived stress (13). Night and shift work have also been found to be associated with poorer lifestyle behaviors and with risk factors of CeVD, such as hypertension and diabetes (17, 18), which may influence the risk. In a recent study of Swedish twins, a higher prevalence of overweight and smoking was observed among individuals who had been exposed to night shift work compared to those with no history of night work, but with no obvious difference in the prevalence of alcohol consumption or leisure-time activity (10).
Shift work is common, especially in the healthcare sector, where the proportion of shift workers (workers with daily split shifts, permanent shifts of mornings, afternoons or nights, alternating or rotating shifts, or other types of shift work) is about 40% (19). In comparison, in the European Working Conditions Survey of 2015, for all sectors combined, 21% reported shift work, 19% reported night work, 16% reported long working hours of >48 hours per week, and 23% reported not having time to recover (<11 hours between working days) (19). Similarly in Sweden, figures for the proportion of shift and night workers for all sectors combined were 21% and 14%, respectively (20).
In a meta-analysis of five cohort studies (21-25) a small increase in stroke mortality was reported among shift workers (7). An increased mortality in cardiovascular disease was observed among Danish nurses, who worked night shifts (8), as well as among night shift workers in a cohort of Swedish twins (10). A systematic review and meta-analysis by Torquati et al (2018) demonstrated a higher risk of cardiovascular disease events among shift workers than day workers, supported by a dose-response relationship (26).
A limitation in several of the previous studies is imprecise exposure data, with self-reported information on working hours and schedules and lack of longitudinal exposure information. This increases the risk of error in classification of exposure and prohibits the possibility to give detailed recommendations to improve the used shift patterns (6, 27, 28). Furthermore, we are not aware of any earlier studies on the association of specific shift work patterns with incident CeVD. An increased understanding of how various aspects of night and shift work (such as frequency of night shifts, consecutive night shifts and quick returns) influence the risk could contribute to knowledge on how work schedules might be optimized to reduce the risks associated with shift work.
The aim of this study was to evaluate the effects of various aspects of night and shift work, regarding incident stroke

and other CeVD, by using detailed and registry-based exposure data.

Methods

Study population

The cohort was identified from a computerized administrative employee register (HEROMA) in Region Stockholm (formerly Stockholm County Council), Sweden. We identified healthcare employees who were employed for at least one year anytime between 1 January 2008 and 31 December 2016. The healthcare provided under the Region Stockholm's management includes both in- and outpatient care services, such as emergency hospitals, local medical centers, family doctors and maternity clinics. We restricted the study to occupational groups with an expected high proportion of night and shift workers, mainly nurses (N=17 238) including midwives, and nursing assistants (N=13 222) including caregivers, accommodation assistants and personal assistants. Unfortunately, it was not possible to obtain precise information on working hours for physicians and therefore they were excluded in this study.

The final CeVD cohort of nurses and nursing assistants consisted of 30 460 employees, 26 667 women and 3793 men, after excluding physicians and employees in occupational groups with an expected low proportion of night work (eg, administrators, cleaners, kitchen assistants, psychologists and physiotherapists) and employees with any CeVD before first employment day (based on data back to 1998) or within the first year of employment. A flowchart for the inclusion and exclusion procedure is presented in figure 1.

Data sources and assessment of the outcome

The information on working hours was obtained from the same computerized administrative employee register (HEROMA) as for the identification of the cohort. From the HEROMA system we collected detailed individual information on working hours day-by-day for all employed from 1 January 2008 to 31 December 2016, including information on occupation and workplace for each working period. For each work shift, there was information on the exact start and end time. Information about education and country of birth was collected from the register of the total population at Statistics Sweden.

Information on the outcome CeVD (I60-69 in ICD10) was retrieved from the national patient register at The National Board of Health and Welfare (inpatient care) for the period 2009-2016 and from the regional database (VAL database) for the period 2009-2017. The VAL database includes diagnoses from both inpatient care and outpatient contacts (health centers, emergency services and hospital visits where the patients have not been hospitalized) within the Region Stockholm. We included the CeVD diagnosis that appeared first in either of the two registers, during the follow-up period 1 January 2009 to 31 December 2016 (N=201), and for the period 1 January 2017 to 31 December 2017 information was available only from the VAL database (N=22). We used incident stroke (I61, I63 and I64 in ICD-10) as a separate outcome. The employees were at risk from one year after the start of employment until CeVD diagnosis, death, or end-of-follow-up, whichever came first.

Classification of exposure

We aggregated the information on working hours from HEROMA to classify persons with respect to different types of shift work and working hours. Shifts <4 hours were not included. The method for classifying working time patterns based on payroll-based daily objective working hours was first evaluated in the Finnish healthcare system (27), and the method for aggregation on working hours from HEROMA was recently described in a study based on the same cohort of healthcare employees as in the present study, but with a focus on shift and night work during pregnancy and risk of preterm birth (29).

All shifts were classified as follows: (i) Daytime work only (starts after 06:00 and ends no later than 18:00 hours), (ii) afternoon shift (starts after 12:00 and ends later than 18:00 hours but not a night shift), (iii) night shift (>3 hours between 22:00-06:00 hours, based on Swedish Working Hours Act). Based on this classification of shifts, the cohort subjects were, for each year, classified as (i) daytime workers, (ii) persons also working afternoon shifts but not night shifts, (iii) persons working various shift types including night shifts, or (iv) persons working night shifts only. The exposure classification was assessed annually to take into account variations over time.

Among all employees, for each year, we defined the frequency of night shifts per year (0, 1-30, >30 times), the

frequency of >3 consecutive night shifts per year (0, 1-15, >15 times) quick returns from night shifts (<28 hours between the end of the night shift and the beginning of the following shift) or from other shifts (<11 hours) per year (0, 1-30, >30 times), and the frequency of long (>45 hours) working weeks per year (0, 1-10, >10 times). We also classified the cumulative number of years with night shifts since 2008 (0, 1-5, >5 years). The cut off points for the aspects of night and shift work and long working weeks were chosen on the basis of a compromise between obtaining a sufficiently large contrast between the exposure categories while not losing power. However, we also conducted analyses based on continuous measures (test for trend).

Data analysis

To assess the effect of different types of shift work and working hours on the risk of CeVD, we used discrete time proportional hazard models, stratifying the persontime experience of the cohort by follow-up year, starting the assessment of risk one year after first employment day (30, 31). In the estimations of hazard ratios (HR), we adjusted for sex, age (continuous), country of birth (Sweden; Nordic countries except Sweden; Europe except Nordic countries; other countries), education (higher education (university >3 years); upper secondary or elementary school or less), and profession (nurses including midwives; nursing assistants including caregivers, accommodation assistants and personal assistants). We adjusted for country of birth since there are differences in CeVD risk with ethnicity, and adjustments for educational level and profession were used as a proxy for socioeconomic status that also affects the risk. Age and exposure variables were treated as timedependent variables updated for each year of follow-up, whereas sex, country of birth, education and profession were fixed. Each of the models per disease was estimated separately. In additional analyses, we also adjusted for the total number of night shifts per year among employees who worked at least one night shift during the year in order to differentiate between the effect of the intensity of night work in general and the effect of different aspects of night shift work such as frequently working consecutive night shifts or having quick returns from night shifts.

We estimated HR with 95% confidence intervals (CI) for CeVD in relation to different aspects of night and shift work (eg, type and frequency of shift work, consecutive shifts, and quick returns) and frequency of long working weeks. For type of shift work, the comparisons were performed with those who always worked day shifts as the reference group. For the other exposure variables, the comparisons were performed with those who worked day and/or afternoon shifts but no night shifts ('never night shifts') or with the lowest exposure category as the reference group. The estimated HR were based on the exposure during the year preceding the outcome, except for analyses of cumulative years of night work.

The test for trend with number of times per year of night shifts and the number of times per year of the different aspects of night and shift work and long working weeks used the arithmetic average of number of times in each exposure category as a continuous variable in the regression model. The test for trend with cumulative number of years with night shifts used the arithmetic average of number of night-years in each exposure category as a continuous variable.

In a sensitivity analysis, we restricted the analysis to employees who ever worked >3 consecutive night shifts in order to explore the effect of different levels of exposure to consecutive night shift work from the effect of general night work. Comparisons were then performed with those with the lowest exposure category of consecutive night shift work as the reference group.

In additional analyses, we analyzed the risk of CeVD among women and men separately.

We used SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) for all statistical analyses.

Results

The baseline characteristics (sex, age, education, country of birth and profession) of the study participants at the inclusion year, by work schedule, are presented in table 1. The baseline characteristics are from the inclusion year but the work schedules are based on all the years the person worked during 2008-2016. There were 6883 employees with permanent daytime work during the whole employment period, 11 192 with shift work but no night shifts, 11 250 with shift work including night shifts (but not only night shifts) and 1135 with only night shifts during the whole employment period. The proportion of younger employees (<40 years) at the inclusion year was higher

among shift workers and night workers who did not work only nights (shift workers without night shifts: 55%, shift workers with night shifts but not only nights: 65%) than among employees with permanent daytime work (25%) or permanent night work (23%) during the whole employment period. The proportion of men as well as employees with country of birth outside the Nordic countries was higher in the two shift work groups and among night workers. The proportion of employees with higher education as well as nurses was lowest (29% and 33%, respectively) among employees who only worked night shifts during the whole employment period.

The 30 460 employees contributed a total of 240 469 person-years. During the follow-up (up to 9 years, mean 4.7 years), there were 223 incident cases of CeVD in the cohort. Of these, 162 cases were first identified from the national patient register and 61 cases from the regional VAL database. The 223 incident CeVD cases included in total 132 cases of stroke of which 115 were ischemic stroke, 16 were hemorrhagic stroke and one was an unspecified cerebral infarction.

Type and frequency of night work

We found that healthcare employees with shift work including night shifts and employees who only worked night shifts tended to have an increased risk of CeVD the following year compared to those with only day work, although not statistically significant (HR 1.46, 95% CI 0.96-2.21 and HR 1.39, 95% CI 0.88-2.21, respectively) (table 2). The risk was more pronounced among employees who frequently worked night shifts (>30 times per year: HR 1.44, 95% CI 1.04-1.99), and who frequently (>15 times per year) worked >3 consecutive night shifts (HR 1.69, 95% CI 1.18-2.42) compared to those who never worked night shifts (table 2). There was a trend of increasing risk estimates with increasing number of times of night shifts (HR for beta 1.003, 95% CI 1.0001.006, ie, the risk increased by 0.3% for each additional night shift), and for increasing number of times of >3 consecutive night shifts (HR for beta 1.018, 95% CI 1.008-1.031, ie, the risk increased by 1.8% for each additional spell of >3 consecutive night shifts) (table 2). The association remained for >3 consecutive night shifts after additional adjustment for the total number of night shifts, with higher risk estimates and a higher risk increase per time but with wider CI (table 3). In a sensitivity analysis restricting the analyses to employees who ever worked >3 consecutive night shifts, the risk was 1.44 (95% CI 0.86-2.43) for employees who frequently (>15 times per year) worked >3 consecutive night shifts, compared to those with a frequency of 1-15 times of >3 consecutive night shifts per year (data not shown).

For the more specific outcome incident stroke, we found similar trends and a statistically significant association among employees who frequently (>15 times per year) worked >3 consecutive night shifts (table 2). In the sensitivity analysis restricted to employees who ever worked >3 consecutive night shifts, the risk of stroke was 1.66 (95% CI 0.81-3.37) for employees who frequently (>15 times per year) worked >3 consecutive night shifts, compared to those with a frequency of 1-15 times of >3 consecutive night shifts per year (data not shown).

Quick returns

We observed that employees who often (>30 times per year) had quick returns (<28 hours) from night shifts had an increased risk of CeVD (HR 1.52, 95% CI 1.10-2.10) the following year compared to those who never worked night shifts. There was a trend of increasing risk estimates with increasing number of times of quick returns from night shifts (HR for beta 1.006, 95% CI 1.0011.011, ie, the risk increased by 0.6% for each additional quick return) (table 2). The association remained for quick returns from night shifts after additional adjustment for the total number of night shifts, with higher risk estimates and a higher risk increase per time but with wider CI (table 3). Quick returns (<11 hours) from other shifts did not increase the CeVD risk (table 2). Associations with incident stroke demonstrated similar trends for quick returns from night shifts although not statistically significant (table 2).

Cumulative number of years with night shifts

For cumulative night work, the analyses were based on exposure information since 2008. We observed an excess risk of CeVD among employees who had worked night shifts for >5 years since 2008 (HR 1.87, 95% CI 1.27-2.77), and there was a trend of increasing risk estimates with increasing number of years of night shift work (HR for beta 1.083, 95% CI 1.031-1.139, ie, the risk increased by 8.3% for each additional year of night work) (table 2). The excess risk among employees with >5 years of night work was also demonstrated in separate analyses of stroke (HR 2.04, 95% CI 1.26-3.28; HR for beta 1.088, 95% CI 1.021-1.159, ie, the risk increased by 8.8% for each

additional year of night work) (table 2).

Frequency of long working weeks

We did not observe an increased risk of CeVD or stroke among employees who often (>10 times per year) had long working weeks of >45 hours, compared to those with working weeks of <40 hours, and there was no trend of increasing risk estimates with increasing number of times of long working weeks (table 2). The sta- tistical power was too low to study the risk of CeVD in association with the frequency of longer working weeks (only 4 cases among employees who often (>10 times per year) had long working weeks of >50 hours).

Sex-related risks

Stratified analyses of the CeVD risk among women (N=26 667) and men (N=3793) separately did not add much information since there were relatively few men in the cohort, generating few cases (36 CeVD cases among men, 187 CeVD cases among women). The results for women separately were thus very similar to those for the total cohort, although with a tendency of slightly higher risks for women than men, and for men the analyses resulted in low numbers and low statistical power (supplementary material, table S1, https://www. sjweh.fi/article/3986).

Discussion

This is a cohort study of Swedish healthcare employees where we used registry-based assessed day-by-day exposure information on working-hours to investigate the association between different types of night shift work and frequency of long working weeks and inci- dent CeVD. We also investigated the risk of stroke. Our main findings were that employees who worked night shifts >30 times per year or who worked >3 consecutive night shifts >15 times per year, had an excess risk of CeVD the following year compared to those with no night work. There was also an excess CeVD risk among employees with >30 quick returns from night shifts per year and among employees with a cumulative exposure of >5 years of night work. We observed a trend of increasing risk estimates for CeVD with increasing number of times of night shifts, times of >3 consecutive night shifts, times of quick returns from night shifts and the number of years of night shift work. Long working weeks of >45 hours >10 times per year did not increase the risk.

Analyses specifically targeting stroke demonstrated similar risks to those for total CeVD. The risk of incident stroke was statistically significantly increased among employees who frequently (>15 times per year) worked >3 consecutive night shifts and among employees with >5 years of night work, supported by a doseresponse pattern. Since the exposure variables frequency of >3 consecutive night shifts and frequency of quick returns from night shifts are correlated to the number of night shifts worked, we performed additional analyses that also adjusted for the total number of night shifts per year. The effect from the different aspects of night shift work was stronger after this adjustment and thus the effect of working consecutive night shifts and having quick returns from night shifts seems to be at least partially separated from the effect of the intensity of night work in general.

We are not aware of any earlier studies on the association of the specific characteristics of shift work - like the intensity of night shifts or quick returns - with CeVD. However, our results are in line with previous reviews and meta-analyses reporting an increased risk of stroke among shift workers. Vyas et al (5) defined shift work as all schedules that were not regular daytime work, also including night work. In the pooled analyses they demonstrated an increased risk of ischemic stroke (based on two studies) and a non-significant increase of CeVD mortality (based on four studies) among shift workers, compared to non-shift workers. Li et al (7) included five cohort studies [of which two were also included in the study by Vyas et al (5)] in a meta-analysis and observed a slightly increased stroke mortality. In a prospective cohort study of Swedish twins, the risk of mortality due to cardiovascular disease (including stroke) was increased among night shift workers, compared to those with no night work, after adjustment for several important risk factors (such as smoking, alcohol consumption, body mass index and physical activity at leisure time) and with higher risk estimates in night workers with a work duration of >5 years (10).

Our findings indicate both subacute effects (within a year of night shift work) and long-term effects (after many years of night shift work) on CeVD risk. All the analyses, except for cumulative number of years with night work, focused on the risk associated with the exposure during the previous year. Since the exposure information was updated yearly, it is possible for participants to be in, eg, the day and/or afternoon shift group one year and the night shift

group another year and vice versa. Our results are thus based on a narrow time window for the exposure (recent exposure) and do not exclude that the participants may have belonged to other exposure categories in previous years.

Based on our study, we cannot determine the underlying mechanisms of the increased risk, although a disturbed circadian rhythm and consequent effects thereof are likely to have an impact. There is previous evidence of an effect on hormones such as cortisol and melatonin from exposure to consecutive night shifts (32-34). Associations have also been observed between recent night and rotational work and the incidence of hypertension (17) (a common risk factor for both ischemic and hemorrhagic stroke), and between shift work and increased use of medications for type-2-diabetes, dyslipidemia and hypertension (18). Sleep deprivation and insufficient recovery, associated to consecutive night shifts and quick returns, could be a possible pathway from night shift work to the increased CeVD risk. Sleep duration is reduced after nights shifts and does not increase with more consecutive night shifts, leading thus to accumulated sleep debt (15). Insufficient time between the shifts (<11 hours) are associated with short sleep duration, increased sleepiness and higher level of perceived stress (13), as well as increased prevalence of shift work sleep disorder (16), although in the present study we only observed an association between CeVD risk and quick returns from night shifts but not from other shifts. Short sleep and insomnia increase the risk for coronary heart disease (35, 36) in some prospective studies, and are associated with several CeVD risk factors like obesity and diabetes (37, 38).

We also found that insufficient recovery after night shifts (<28 hours) was associated with an increased risk of CeVD. Employees, who perceived incomplete recovery from work during free weekends had an elevated risk of cardiovascular death in a 26-year follow-up (39). Disturbed sleep could even be a common pathway connecting both night and shift work, extended workhours, and work stress to adverse cardiovascular health (11).

We did not find an association between frequent (>10 times per year) long working weeks (>45 hours) and CeVD risk in this cohort, but our study does not rule out an elevation of CeVD risk of frequent very long working weeks of >50 hours. Other studies have found evidence for a relation between average long weekly working hours of >55 hours and incident stroke, compared to those who worked 35-40 hours per week (6, 9).

Strengths and limitations

The major strengths of this study include the large and prospective cohort dataset and the objective exposure data from employee registers. The exposure data is very detailed with individual day-to-day information on different types of shift work and working hours. No data needed to be obtained from the employees themselves, which eliminates the risk that people will forget details about their working hours back in time. Also, the so-called "recall bias" can be avoided since the classification of exposure is not adversely affected by the outcome. Other strengths are that the cohort entirely consists of employees within the healthcare sector, where the percentage of night shift workers is high, and that the data on health outcomes are retrieved from registers of good quality. Another advantage is that we were able to collect information on cases not only from hospital care but also from outpatient visits, ie, we did not miss cases among those who have only received outpatient treatment.

A limitation of the study is that we do not have information on important individual risk factors for CeVD, such as smoking habits and other lifestyle factors, or information on work stressors, such as job strain. These could be confounders or mediators. However, the study is conducted on a cohort of nurses and nursing assistants, which is a more homogenous socioeconomic group than the population as a whole. Therefore, the potential differences in lifestyle risk factors and job strain are probably not so pronounced.

There is also a risk of underestimating the negative effects of night work by the so-called "healthy worker effect" among employees who are working night shifts. Such an effect could, for example, occur if employees with health problems already at the time of entering working life choose not to work at night or if employees are transferred from night work to day work due to a medical condition. In Sweden there is a legal requirement that employers must offer medical checks for night workers at the start of the employment and then regularly, although it is not always complied with (40). However, there may also be a selection into night shift work of employees with unfavorable risk factor profiles (41). Due to the medical checks, the "healthy worker effect" among night workers is probably stronger

than the selection into night work of employees with unfavorable risk factor profiles, and therefore our findings might possibly underestimate the actual risk.

We made additional analyses for men and women separately. However, the relatively low proportion of men (12.5%) in the cohort reduced the statistical power to detect an effect among men separately. For women, the effect was similar as for the total cohort.

Concluding remarks

In conclusion, using registry-based day-by-day exposure information in this cohort of 30 460 Swedish healthcare employees, we have shown that the risk of CeVD among nurses and nursing assistants is associated with night shift work. The number of years with night shift work, the frequency of night shifts per year, the frequency of consecutive night shifts, and time for recovery after night shifts influenced the risk. We believe that work schedules aiming at minimizing these aspects of night shift work may reduce the risk. However, it is important that advice on preventive measures includes also protection against other potential adverse health effects of night and shift work, such as eg, heart disease, cancer, adverse effects on pregnancy outcome and work-related accidents. We hope that future research in this area can contribute information as a basis for overall advice that covers other potential health effects as well.

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Sidebar

This prospective cohort study showed an excess risk of cerebrovascular disease among employees who the preceding year worked night shifts >30 times, >3 consecutive night shifts >15 times, had >30 quick returns (<28 hours) from night shifts, or with >5 years of night work. Work schedules aiming at minimizing these aspects of night shift work may reduce the risk.

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Key terms: cerebrovascular disease; healthcare; night work; occupational exposure; occupational health; prospective cohort study; shift work; shift worker; Stockholm; stroke; Sweden

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Additional material

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Changes in melatonin and sex steroid hormone production among men as a result of rotating night shift work – the HORMONIT study

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ABSTRACT (ENGLISH)

Objective Data from real world settings on circadian disruption and subsequent hormone-related changes may explain the higher risk of hormone-dependent cancers among night shift workers.The present study examines the melatonin and sex steroid hormone levels among night shift workers. Methods We included 44 male, rotating shift workers from a car factory in Spain, sampled both at the end of a 3-week night shift (22:00-06:00 hrs) and a 3-week early morning shift (06:00-14:00 hrs). Participants collected all urine voids over 24-hours during each shift. Urinary concentrations of sex steroid hormones (estrogens, androgens and progestogens) and 6-sulfatoxymelatonin (aMT6s, major melatonin metabolite) were determined. Individual cosinor analysis was used to derive the acrophase (peak time) and area under the curve (total production). Linear mixed models examined intraindividual associations between night shift work and log-transformed 24-hour peak time and total production of hormones compared to early morning shift work. Results The acrophase was delayed during the night shift for aMT6s [geometric mean difference (GMD) 7.53 hrs, 95% confidence interval (CI) 4.46-10.60], androgens (eg, testosterone: GMD 6.83 hrs, 95% CI 0.34-13.32) and progestogens (eg, 17-hydroxyprogesterone: GMD 4.54 hrs, 95% CI 2.92-6.16) compared to the early morning shift. We found a higher production of adrenal androgen 11-oxoandrosterone/11-oxoetiocholanolone [geometric mean ratio (GMR) 1.43, 95% CI 1.12-1.81], and a lower production of adrenal progestogen 16-cysteinylprogesterone (GMR 0.79, 95% CI 0.67-0.93) during the night shift compared to the early morning shift levels. Conclusions Night shift work was associated with melatonin and sex hormone-related changes in timing and total production, providing insight into the mechanistic path for its association with hormone-dependent cancer.

FULL TEXT

Headnote
Objective Data from real world settings on circadian disruption and subsequent hormone-related changes may explain the higher risk of hormone-dependent cancers among night shift workers.The present study examines the melatonin and sex steroid hormone levels among night shift workers. Methods We included 44 male, rotating shift workers from a car factory in Spain, sampled both at the end of a 3-week night shift (22:00-06:00 hrs) and a 3-week early morning shift (06:00-14:00 hrs). Participants collected all urine voids over 24-hours during each shift. Urinary concentrations of sex steroid hormones (estrogens, androgens and progestogens) and 6-sulfatoxymelatonin (aMT6s, major melatonin metabolite) were determined. Individual cosinor analysis was used to derive the acrophase (peak time) and area under the curve (total production). Linear mixed models examined intraindividual associations between night shift work and log-transformed 24-hour peak time and total production of hormones compared to early morning shift work. Results The acrophase was delayed during the night shift for aMT6s [geometric mean difference (GMD) 7.53 hrs, 95% confidence interval (CI) 4.46-10.60], androgens (eg, testosterone: GMD 6.83 hrs, 95% CI 0.34-13.32) and progestogens (eg, 17-hydroxyprogesterone: GMD 4.54 hrs, 95% CI 2.92-6.16) compared to the early morning shift. We found a higher production of adrenal androgen 11-oxoandrosterone/11-oxoetiocholanolone [geometric mean ratio (GMR) 1.43, 95% CI 1.12-1.81], and a lower production of adrenal progestogen 16-cysteinylprogesterone (GMR 0.79, 95% CI 0.67-0.93) during the night shift compared to the early morning shift levels. Conclusions Night shift work was associated with melatonin and sex hormone-related changes in timing and total production, providing insight into the mechanistic path for its association with hormone-dependent cancer.
Key terms circadian; night work; rotating shift work; shift worker.
Internal biological processes are regulated by a central "clock" in the suprachiasmatic nuclei in the brain and peripheral clocks in virtually all tissues. These clocks dictate the rhythm of many human biological processes, including hormone production (1, 2). These rhythms can be influenced by external factors, such as light, a major environmental cue leading to the synchronization of endogenous circadian rhythms to the 24-hour day (3).
With approximately 19% of the European population working atypical hours including work during the night (4), and the expansion of human activities over the 24-hour day, examining the impact of circadian misalignment on health is an important priority. In 2007 and again in 2019, the World Health Organization's International Agency for Research on Cancer (IARC) determined that shift work is "probably carcinogenic to humans," (Group 2A) based on sufficient evidence from experimental animal models but limited human, epidemiological and mechanistic evidence (5) (6). IARC also concluded that there were too few studies and inconsistent results to comment on the evidence of sex steroid hormone alterations, especially among men (6).
Experimental evidence shows that circadian disruption due to night shift work is associated with a wide range of diseases, including cancer, cardiovascular diseases, and metabolic disorders (7, 8). Multiple epidemiological studies have examined changes in melatonin among night shift workers (9), however fewer studies have focused on sex hormone-related changes in this population (1, 10, 11). Sex steroids have wide-ranging impacts, including influencing cancer development and progression (12). Prostate cancer, the most common cancer among men, is hormone-dependent (13), and there is mounting evidence of an association between night shift work and this cancer (14-16). A possible mechanism to explain the elevated prevalence of hormone-related cancers among night shift workers may be through the light-induced suppression of melatonin and alterations in sex steroid hormone rhythms (17-20).
Studies that have examined melatonin and sex steroid hormone changes among night shift workers have included populations with permanent night shift work (1) or fast rotating night shift work (10, 11) compared to permanent day shift workers, with findings suggesting that sex-hormone rhythms, as well as melatonin rhythms, varied with different shift schedules and light conditions (1, 3). Furthermore, most previous studies have compared hormonal production between subjects rather than focusing on individual changes within each participant (1, 3, 10, 11).
The HORMONIT study aimed to evaluate hormonerelated changes in melatonin and sex steroids in a population of male rotating shift workers working both day and night shifts in a slow backward rotation. We hypothesized that night shift work would be associated with changes in the timing and total production of melatonin and sex steroid

hormones.

Methods

Study population

This study included male rotating shift workers from a car factory in Barcelona, Spain. Workers rotated backwards (counterclockwise) through shifts: night shift (22:00-06:00 hrs), evening shift (14:00-22:00 hrs), and early morning shift (06:00-14:00 hrs). The majority of workers were assembling/mounting car parts, while others were supervisors, painters or polishers and drivers. Workers worked five-day work weeks (Monday-Friday) with two days off (Saturday and Sunday). Workers completed a given shift in 3 week stretches before switching to a different shift. After the 3-week rotation, they began the next rotation with no extra time off besides the standard weekend. We collected data from participants twice. The first time point of sample collection occurred when participants were working an early morning shift near the end of their 3-week early morning shift rotation (2nd or 3rd week). The second point of sample collection occurred when participants were working a night shift near the end of a 3-week night shift rotation (2nd or 3rd week). We did not collect samples from participants on Mondays to avoid some potential shifting of circadian rhythms due to nighttime sleeping during the weekend days off.

To be eligible for the study, participants had to be 18-65 years of age. We excluded participants with a prior history of cancer. The Parc de Salut Mar Clinical Research Ethics committee approved the study (#2015/6351). Participants received a leaflet with study information, and all participants signed an informed consent form. A total of 71 men volunteered for this study. After checking eligibility criteria, 7 participants were found to be ineligible and 8 withdrew prior to study start due to the time commitment involved. Ultimately, 56 participants were enrolled in the study, of whom 51 completed all parts of data collection. From the 51 participants, 7 lacked complete melatonin and sex steroid hormone data at both time points, resulting in 44 participants who had complete data and were included in the present analyses (supplementary material, www. sjweh.fi/article/3991, figure S1).

Exposures

At the start of the early morning shift, participants were interviewed and data on demographics, work-related information, smoking, alcohol, caffeine, dietary habits, medical history and medication use, and sleep-related information were collected.

Light exposure assessment

In addition to questionnaire-collected data, each participant was given a light sensor (HOBOware, Onset Computer Corporation). Similar to a previous study by Papantoniou et al (3), participants wore a HOBOware light intensity data logger that continuously recorded their ambient light exposure every 12-15 seconds over an approximate 24-hour period corresponding to the days when participants collected urine. The logger was relatively small in size (5.8 x 3.3 x 2.3 cm) and light in weight (18 g) and was worn at shoulder level in order to obtain measurements of light that would approximate the amount of light reaching the retina. During sleep, par- ticipants were instructed to place the logger on a bedside table with the sensor facing upwards and while showering, participants were instructed to leave the logger nearby in the bathroom again with the sensor facing upwards. The loggers recorded relative light intensity within the range of 0-320 000 lux and were designed for indoor and outdoor settings. Overall, the mean and median 24-hour light exposure as well as mean and median light exposure during working hours were estimated.

Outcomes

Participants provided urine samples from all natural urine voids over an approximate 24-hour period on two separate working days (one during the night shift and one during the early morning shift). Participants collected urine samples in 50 mL plastic tubes, labeled with the time and date of each collection. We advised participants to keep the urine samples in a refrigerator immediately after collection and to send them to the receiving laboratory by courier mail 1 or 2 days later. The urine aliquots for aMT6s analyses were stored at -80°C and the aliquots for steroid analyses were stored at -20°C until analyses. A total of 682 urine samples were collected and analyzed. During the early morning shift, participants collected a median of 7 (interquartile interval 6-8) urine samples, and during the night shift a median of 7 (interquartile interval 6-9) samples were collected. We required participants to have >4 urine samples during each 24-hour day. This resulted in the exclusion of early morning shift hormone data for 3 participants and

night shift hormone data for 2 participants.

Determination of the levels of sex steroid hormones, their main metabolites, and enzymes

Urinary concentrations of sex steroid hormones (androgens, estrogens and progestogens) and their main metabolites were determined by liquid chromatography tandem mass spectrometric (LC-MS/MS) methods previously developed in our group (21-23). The activity of several related enzymes was estimated using the ratio between the metabolite and the hormone concentrations (supplementary table S1). A global estimation of the metabolism was also estimated by dividing the levels of each hormone by the sum of all its corresponding metabolite levels. Specifically, we examined androgen hormones, metabolites and related enzymes (12 analyzed), progestogen hormones and metabolites (5 analyzed), and estrogen hormones, metabolites and related enzymes (4 analyzed).

Urinary concentrations of sex steroid metabolites (excreted as both unconjugated and glucuronoconjugated) were determined based on a previously validated method (22). Briefly, urine (0.5 mL) was mixed with 50 pL of the internal standard solution, 0.5 mL of sodium phosphate buffer (1M, pH 7) and 30 pL of ß-glucuronidase from E. coli. After hydrolysis (1 hour at 55 °C), 2 mL of saturated sodium chloride solution, 250 pL of 25% of potassium carbonate and 6 mL of ethyl acetate were added and a liquid-liquid extraction was performed. The organic layer was extracted and evaporated to dryness (40 °C, <15 psi). Dried extracts were reconstituted with 150 pL of water: methanol (9:1) and 10 pL were injected into the LC-MS/MS system. The limit of detection of the method was in the range 0.2-10 ng/mL and the coefficient of variation (CV) at three concentration levels were in the range 80-120%. Intra- and inter-day precisions typically <20% were obtained for the detection of urinary steroids (22).

Urinary steroid cysteinyl metabolites were determined as previously reported (23). Briefly, 0.5 mL of urine was mixed with 50 pL of the internal standard (methandienone, 1 pg/mL), and basified by addition of 300 pL of potassium hydroxide (6 M). The mixture was heated at 60 °C for 15 minutes, followed by a liquid-liquid extraction with 6 mL of tert-butyl methyl ether. The organic layer was separated and evaporated. The residue was dissolved into 150 pL of a mixture of water:acetonitrile (1:1, v/v) and 10 pL were injected into the LC-MS/MS system. The limit of detection of the method was in the range 0.001-0.05 ng/mL and the CV% at three concentration levels were in the range 85-115%. Intra- and inter-day precisions typically <20% were obtained for the detection of urinary steroid cysteinyl metabolites (23).

Determination of the levels of aMT6s

We also measured urinary 6-sulfatoxymelatonin (aMT6s) concentrations, the major melatonin metabolite by radioimmunoassay (Stockgrand Ltd, University of Surrey, UK) (24). Urine samples were analyzed in duplicate and all samples from the same participant were included in the same assay. The inter-assay coefficients of variation were 6.9% at 2.4 [± standard deviation (SD)] 0.2 ng/mL, 7.6% at 11.3 ±SD 0.9 ng/mL, and 6.9% at 21.1 ±SD 1.4 ng/mL. Limit of detection was 0.33 ng/ml.

Determination of the levels of creatinine

Creatinine levels were determined in all urine samples by the same laboratory (Stockgrand Ltd, University of Surrey, UK). Levels were determined automatically using an IL600 analyzer (Randox Laboratories Ltd, UK). The limit of detection of the assay was 1.5 mmol/L and interassay variability was 3.2% at 6.95 ±SD 0.22 mmol/L and 3.8% at 14.01 ±SD 3.78 mmol/L. All aMT6s values and sex steroid metabolites were creatinine standardized and reported as ng metabolite/ mg creatinine.

Covariates

We examined within-person variations in hormone levels for the early morning shift period versus the night shift period. Because of this within-person comparison approach, adjustment was not required for many covariates traditionally adjusted for in shift work circadian rhythm studies. However, variation in daylight hours is known to impact circadian rhythms (25, 26). Because urine samples were taken at two time points, that in some cases differed by several weeks (median 45 (±SD 43) days), we adjusted analyses for length of daylight (using values available from the National Oceanic and Atmospheric Association calculator and inputting the latitude 41o 230 N and longitude 2o 100 E for Barcelona) (27).

To define chronotype in our study, the aligning of an individual with greater morningness or eveningness tendencies

(28), participants responded to the Munich Chronotype Questionnaire for shift workers (MCTQShift) (29) both at the beginning of an early morning shift and at the beginning of a night shift. Chronotype (MSFcorr) was estimated as the mid-sleep time on free days (MSF = [sleep onset on free day + sleep duration on free day]/2), corrected for oversleep on free days compared to working days (MSFcorr = MSF - [sleep duration on free day-sleep duration on a working day]/2). Sleep duration was calculated from patient reported sleep onset and offset. We assessed chronotype as a categorical variable where categories were built using tertiles of the distribution in our population [morning type: MSF <04:00 hr, neither type: MSF (04:00-04:50) hr, evening type: MSF >04:50 hr] (30).

Statistical analysis

We compared within-participant hormone levels during the night shift period to hormone levels collected during the early morning shift period as the reference.

To evaluate the rhythm of all hormones and their metabolites, we applied individual cosinor analysis, a procedure for fitting a sinusoidal curve. This method extrapolates values of hormones collected throughout the 24-hour day to plot the full diurnal rhythm of a given hormone or metabolite for participants (31). For each participant, we derived the acrophase (peak time), mesor (24-hour mean), amplitude (doubling the amplitude is a measure of the extent of predictable change within a cycle) and the area under the curve (AUC, total production) of the metabolites (32). To check the cosinor-derived parameters, we examined the percentage of variability accounted for by the cosine curve (100% indicates that all data points fall on the cosine curve, supplementary tables S2 and S3). 6-Sulphatoxymelatonin and the majority of the steroid hormones and metabolites had moderate or higher fits. However, in some cases for a given participant and shift, the R-squared values indicated low fits. We described the 24-hour total production [geometric mean (GM) and SD] and peak time [GM and 95% confidence interval (CI)] for all outcomes in participants both during their early morning shift and during their night shift.

Using generalized linear models, we examined associations between shift work schedule and log-transformed 24-hr peak time (acrophase) and total production. We applied log transformation to achieve a normal distribution of the variables. Then, we applied linear mixed models to evaluate the differences in the acrophase (presented as geometric mean differences [GMD]) and the AUC (presented as the geometric mean ratio [GMR]) of hormones and their metabolites comparing the values from the night shift to those from the early morning shift.

Additionally, we examined if there was evidence of effect modification for the aMT6s results based on chronotype (morning type, evening type, neither type), categories of self-reported cumulative duration (years) of night shift work history, or based on level of light exposure (low, moderate, high) during work hours of night shift work from light sensor data. For cumulative duration of night shift work history, we created two categories based on the population mean exposure time (table 1). For level of light exposure during night shift work hours, we created these categories based on tertials of the population median exposure levels (low: median 37.0 (IQR 30.9-40.5), moderate: median 63.2 (IQR 53.7-72.6), high: median 114.6 (IQR 94.7-156.8). To examine if there was evidence of effect modification, we introduced an interaction term into the model and reported effect estimates across different chronotypes, categories of cumulative duration of night shift work history, and light exposure levels during night shifts.

Finally, because some participants were sampled during the 2nd week and others in the 3rd week and because the day of sample collection (Tuesday-Friday) during a given week differed between participants, we conducted some sensitivity analyses. The week of the shift (2nd or 3rd) would mean that participants would potentially be more or less adapted to their shift schedule, and the distance from the weekend (Tuesday-Friday) may similarly influence hormone levels based on for example possible sleep habit differences on a weekend versus a work day. To examine these factors, we reported estimates from a) an analysis that adjusted for the day of the shift the participant was in at the time of sampling (1-21 days with the first Monday of that shift considered day 1) and b) an analysis that adjusted for the number of prior consecutive days of that shift (ie, if sampled on a Wednesday, the number of prior consecutive days of the shift would be 2 since the weekend).

Results

The mean age of the population was 38 (SD 8) years, and participants had worked night shifts for 10 (SD 6) years. More than half of the population had a BMI >25 kg/m2 (55%) and were former or current smokers (57%). The

average light exposure during work on an early morning shift was 913 (SD 1396) lux while during a night shift the corresponding value was 78 (SD 58) lux. Sample collections were done on an early morning shift among 37 participants (84%) while 7 (16%) participants' samples were collected on a night shift. Samples were collected for participants at a median of 17 days into the 21-early morning shift rotation (IQR 16-18) for the day shift and on the 16th (IQR 16-17) day of the night shift. Furthermore, participants had worked a median of 2 (IQR 2-3) consecutive days prior to when the early morning shift samples were collected and a median of 2 (IQR 1-2) consecutive days prior to when the night shift samples were collected. The average time between when participants collected data during the early morning shift period and when they collected data during the night shift period was 45 (SD 43) days (table 1).

In analyses adjusted for hours of daylight, we observed a later acrophase peak in aMT6s during the night shift compared to the early morning shift (supplementary figure S2). In addition, the acrophase shifted for aMT6s during the night shift compared to the early morning shift (GMD 7.53, 95% CI 4.46-10.60) (table 2, figure 1). We also examined changes in overall hormone and metabolite levels, using the AUC values. The total production of aMT6s was lower in samples collected during the night shift (GMR 0.89, 95% CI 0.78-1.01) compared to during the early morning shift, but this difference did not reach statistical significance (table 3, figure 2).

In addition to changes in aMT6s, we observed a later acrophase peak in sex steroid hormones and their metabolites during the night shift compared to the early morning shift (supplementary figure 2). The acrophase was shifted for several androgens: testosterone (GMD 6.83, 95% CI 0.34-13.32), epitestosterone (GMD 7.54, 95% CI 3.09-12.00), androstenedione (3.60, 95% CI 1.13-6.08), androsterone (GMD 3.72, 95% CI 0.556.89), etiocholanolone (GMD 3.18, 95% CI 0.88-5.48) and 7-cysteinyltestosterone (2.30, 95% CI 0.18-4.42), and several progestogens: 16-cysteinylprogesterone (GMD 3.03, 95% CI 0.93-5.13), 17-hydroxyprogesterone (4.54, 95% CI 2.92-6.16), and 17-hydroxypregnanolone (GMD 2.19, 95% CI 0.33-4.05) (table 2, figure 1). There was no association between night shift work and the acrophase of estrogens. When examining the total production of sex steroid hormones, we observed a higher production of 11-oxoandrosterone/11-oxoetiocholanolone (GMR 1.43, 95% CI 1.12-1.81), and a lower production of 16-cysteinylprogesterone (GMR 0.79, 95% CI 0.67-0.93) during the night shift compared to their early morning shift levels (table 3, figure 2).

In our analyses examining possible effect modification in aMT6s levels during the night shift compared to the early morning shift by chronotype, cumulative night shift work history and light during night work, our results suggested that those with greater levels of light exposure during night shifts experienced a larger shift in acrophase during the night shift (GMD 7.32, 95% CI 4.18-10.47 for low light, GMD 8.60, 95% CI 4.68-12.52 for moderate light and GMD 10.70, 95% CI 5.67-15.64 for high light). We also found that those with greater levels of light exposure during the night shifts experienced lower levels of aMT6s production compared to the early morning shift (GMR for high light exposure 0.73, 95% CI 0.60-0.88 compared to GMR 0.89, 95% CI 0.73-1.07 and GMR 1.01, 95% CI 0.83-1.22 for moderate and high light, respectively) while those with a shorter duration of night shift work history did not have a difference in total production of aMT6s (supplementary table S4). There was no evidence of differences in aMT6s production during the night compared to the early morning shift based on chronotype or cumulative duration of prior night shift work.

Finally, results from the two sensitivity analyses with additional adjustment for the day number of the shift and the number of prior consecutive days in the shift produced results similar to the primary analyses (supplementary table S5 and S6).

Discussion

In this study of slow, backward rotating shift workers, the acrophase time of aMT6s, androgens and progestogens were significantly delayed during the night shift compared to the early morning shift. Alterations in the total production of several hormones were also apparent.

We found that the acrophase of aMT6s was delayed by several hours (4.5 hours) during the night shift work period. The phase shift of aMT6s between the early morning and night was found to be larger among participants who had greater levels of light exposure during night shift work, which is in agreement with previous studies (3, 33, 34). In an

earlier study, the acrophase of melatonin was shifted by 3 hours (3). Furthermore, in the present study, overall aMT6s production was slightly lower during night shifts than early morning shifts, however the effect estimate was not pronounced. In the earlier study (3), aMT6s production was decreased among night shift workers with a mean production that was 33% lower among night shift workers compared to day shift workers. In the present study, total aMT6s production levels were somewhat lower (10%), but CI overlapped one (3). Several aspects should be considered when comparing results from the present study to other melatonin biomarker studies in night shift workers. Firstly, the population in the present study worked in slow rotating shifts, with samples collected during the second or third week of a 3-week rotation. This was done because we were interested in examining how hormone levels and timing were altered after adaptation to the shift schedule sets in to some degree. Previous research suggests that extended periods of night shift work are needed to achieve adaptation (35, 36), though many individuals do not appear to be capable of complete adaptation (37). Slow rotating shifts are very different from fast rotating shifts, such as those included in our earlier research (1, 3) and are expected to influence hormone rhythms to a different degree because of adaptation to the shift schedule. An additional consideration should be given to the timing of the shifts. It is possible that because our reference group was an early morning shift (beginning at 06:00 hrs) while the other analysis included a less extreme day shift comparison, that we may observe a larger acrophase delay because the contrast between night and early morning is bigger than the one between a day and night shift. However, in any case, the change in aMT6s between night and early morning workers is important because melatonin is a major driver of circadian rhythms, and it also has anti-cancer properties (38, 39). Because of this, alterations in melatonin production among night shift workers is a suggested key pathway explaining the carcinogenicity of shift work.

In the present study, the acrophase of many androgen hormones, metabolites and androgen-related enzymes was shifted during the night shift compared to the early morning shift. There is limited prior epidemiological literature focusing on the circadian rhythm of androgens among male night shift workers. Androgens are widely implicated in cancer progression, with research showing that androgen deprivation is accompanied by tumor regression (40). Besides the phase shift for many of the steroids examined, there was over production of the main metabolites of 11-oxygenated androgens (11-oxoandrosterone/11-oxoetiocholanolone) during the night shift. These adrenal-derived androgens have emerged as major components of several disorders (4143). Among these disorders, 11-oxygenated androgens are the predominant circulating androgens in castration resistant prostate cancer (CRPC) (44), and they are the preferred substrate for AKR1C3 (an enzyme that catalyzes the reduction of weak androgens to more potent androgens), which is increased in CRPC tumors (45). Thus, 11-oxygenated androgens have been identified as key components in the development and progression of castration resistant prostate cancer (46, 47). Our results pointed to an over production of these androgens during the night-shift, suggesting a potential mechanism between night-shift and prostate cancer development and progression.

We also found changes in the acrophase of several progestogens and a lower production of the adrenal progestogen 16-cysteinylprogesterone warranting further study of progestogens among male night shift workers. Several prior studies have examined changes in these hormones among female night shift nurses, with results showing higher levels of estrogen and progesterone among women working rotating night shifts compared to day shift workers (11). While progesterone has been extensively studied in relation to female cancers, progesterone also has essential functions in male physiology, and the presence of progesterone receptors has been confirmed in several cancers, including prostate cancer (48). Furthermore, the co-expression of steroid hormone receptors in hormone-dependent cancers is widespread and these receptors may interact to a large degree, possibly impacting tumor growth and progression. In the present study, estrogen levels were unchanged during the night shift period. Both 11-oxoandrosterone/11-oxoetiocholanolone, which was over produced during the night shift, and progestogen 16-cysteinylprogesterone, which was under produced during the night shift, are adrenal-derived steroids (21, 46), suggesting that the production of adrenal steroids is altered by night shift work. The adrenal gland plays a pivotal role in CRPC as evidenced by the relevance of adrenal-derived androgens (46, 47) and by suppression of tumor growth in animal models by surgical adrenalectomy (49). The essential role of the adrenal peripheral clock in

harmonizing the rhythm of adrenal glucocorticosteroid production is well established (50, 51). However, the influence of this clock in the production of adrenal androgens/progestogens and its consequences in health and disease are as yet poorly understood and require further investigation.

There are some limitations of the present study including the small sample size, however, by having repeated measures for each participant this was mitigated to some extent. In addition, the reference samples came from workers engaged in early morning shift work. These participants began work early (at 06:00 hrs), and we expect hormone levels measured during these early morning shifts were also altered in part by this early work start time and do not fully represent the natural 24-hour rhythm that may be seen if our comparison group had included participants working more traditional hours who did not have to wake up so early for a morning shift. Additionally, we have extrapolated steroid production by measuring urinary metabolites. This strategy might underestimate alterations in metabolism as underlying cause of the observed alterations. Finally, the HOBO light logger has been found to underestimate light at low light levels and therefore the light levels during the night shift in secondary analyses may not be as low as reported. This study also has several strengths including the collection of all urine voids during 24 hours (approximately 7) and many parameters that are important for circadian research including light exposure, chronotype and information on prior shift work history. In addition, by comparing participants to themselves, we minimized confounding.

In conclusion, night shift work was associated with a delay in the peak time of aMT6s and several sex hormones as well as being associated with changes in total hormone production of androgens and progestogens. These findings provide further insight into mechanistic pathways that may explain the association of night shift work with prostate or other hormone-dependent cancers.

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Conflicts of interest

JMN, PSF and AT work at the Occupational Health service of the car factory, which was the setting of the present study. Within the HORMONIT study working group they express their own views and do not represent the company.

Sidebar

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DETAILS

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Screening for cognitive impairment among patients with work-related stress complaints in Denmark: validation and evaluation of objective and self-report tools

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ABSTRACT (ENGLISH)

Objective Many patients with work-related stress display cognitive impairment that may hamper recovery. We examined objective and subjective tools for screening of cognitive impairment in this patient group. Methods Patients were assessed with Danish versions of the objective Screen for Cognitive Impairment in Psychiatry (SCIP-D), standardized neuropsychological tests that tapped into the same cognitive domains, the self-assessed Cognitive Failure Questionnaire (CFQ), and several additional scales of symptom severity and psychosocial status. Concurrent validity of the SCIP-D and CFQ was assessed by calculation of Pearson's correlation coefficients between the objective and subjective tools and the scores on more conventional standardized neuropsychological tests. Decision validity was assessed with logistic receiver-operating-characteristic analyses using a cut-score approach to the objective and the subjective test results to predict impairment detected by the standardized tests.

Cognitive norms were established through the data of 79 healthy controls. SCIP-D scores were compared between patients and healthy controls with independent t-tests. Results We included 82 patients with work-related stress. The SCIP-D total scores were strongly associated with standardized neuropsychological tests (r=0.76, P<0.001). The self-assessed CFQ was not associated with either measure of objective cognitive functioning (r<0.12, P>0.30). The optimal SCIP-D total-score cut of <72 identified 43.2% of the patients with global objective cognitive impairment. The patients performed mildly-to. moderately lower than the healthy controls on the SCIP-D total score (Cohen's d=0.39) and the subtests for working memory (d=0.39) and processing speed (d=0.61). Conclusion The SCIP-D is a valid screening tool sensitive to objective performance-based cognitive impairment among patients with work-related stress.

FULL TEXT

Headnote

Objective Many patients with work-related stress display cognitive impairment that may hamper recovery. We examined objective and subjective tools for screening of cognitive impairment in this patient group. Methods Patients were assessed with Danish versions of the objective Screen for Cognitive Impairment in Psychiatry (SCIP-D), standardized neuropsychological tests that tapped into the same cognitive domains, the self-assessed Cognitive Failure Questionnaire (CFQ), and several additional scales of symptom severity and psychosocial status. Concurrent validity of the SCIP-D and CFQ was assessed by calculation of Pearson's correlation coefficients between the objective and subjective tools and the scores on more conventional standardized neuropsychological tests. Decision validity was assessed with logistic receiver-operating-characteristic analyses using a cut-score approach to the objective and the subjective test results to predict impairment detected by the standardized tests. Cognitive norms were established through the data of 79 healthy controls. SCIP-D scores were compared between patients and healthy controls with independent t-tests. Results We included 82 patients with work-related stress. The SCIP-D total scores were strongly associated with standardized neuropsychological tests (r=0.76, P<0.001). The self-assessed CFQ was not associated with either measure of objective cognitive functioning (r<0.12, P>0.30). The optimal SCIP-D total-score cut of <72 identified 43.2% of the patients with global objective cognitive impairment. The patients performed mildly-to. moderately lower than the healthy controls on the SCIP-D total score (Cohen's d=0.39) and the subtests for working memory (d=0.39) and processing speed (d=0.61). Conclusion The SCIP-D is a valid screening tool sensitive to objective performance-based cognitive impairment among patients with work-related stress.

Key terms assessment; attention; burnout; exhaustion disorder; memory; neuropsychological test; SCIP; selfrated health; working memory.

Prolonged work-related stress has vast personal, economic, and societal costs as it may impede functional and work capacity (1). In Nordic countries and The Netherlands, occupational clinics manage work-related stress to promote recovery and labor market attachment. Many patients exposed to long-term stress report memory and concentration difficulties (ie, cognitive impairment) as a core feature in addition to symptoms of depression, anxiety, fatigue, sleep problems, and social withdrawal (2, 3). As most modern jobs require complex cognitive skills, it is likely that consideration of cognitive impairment in clinical management of workrelated stress may improve occupational recovery, eg, when discussing strategies for cognitive remediation, adjustments of job tasks, and the optimal time for return to work (4-7).

Since the mid-2000s, there have been several reports of mildly-to-moderately impaired performance on neuropsychological tests for verbal learning and memory, executive functioning, processing speed, and attention in patients with work-related stress (2, 8-10). Longitudinal studies suggest that subjectively selfreported and objectively measured cognitive impairments may persist several years after seeking healthcare support (10, 11). Indeed, growing evidence indicates no or weak association between subjective and objective measures of cognitive impairment in this patient group (8, 12, 13). A recent systematic review on age-related cognitive decline concluded that studies employing more comprehensive self-report measures of cognitive impairment were more likely to detect

objective cognitive impairment (14).
In Danish occupational clinics, neuropsychological functioning is not routinely examined in patients with work-related stress, as such assessment requires resource-consuming procedures conducted by specialized staff. Considering the potential value of improved efforts to enhance recovery, there is a need for optimizing systematic assessment of cognitive impairment by virtue of a brief and inexpensive screening tool suitable for reliable administration after a relatively brief period of professional training.
The Screen for Cognitive Impairment in Psychiatry (SCIP) is a feasible objective cognitive screener (15) that has been validated with good psychometric properties among psychiatric populations in several languages (15-17), including Danish (SCIP-D) (18, 19). The SCIP-D exists in three parallel versions for longitudinal monitoring and consists of five subtests assessing verbal memory, working memory/executive skills, and visuomotor processing speed. The subscale raw scores can be summed to provide a total score to quickly offer an index of global cognitive impairment. Given the symptomatic similarities between patients with work-related stress and affective disorders, the SCIP-D is a promising tool to screen for cognitive impairment in several cognitive domains relevant to patients with work-related stress.
Further, the 25-item self-report Cognitive Failure Questionnaire (CFQ) is a comprehensive well-validated global trait measure of subjective cognitive difficulties in daily life (eg, at work) covering deficits in memory, planning, forgetting names, attention, and motor function (20). The CFQ has shown only weak correlations with social desirability and neuroticism, but strong associations with psychological strain (20, 21). Patients with work-related stress have previously reported higher CFQ total scores [mean 54.4, standard deviation (SD) 14.1] than healthy controls (HC) (mean 24.9, SD 10.8) (2), and there have been preliminary reports of associations with attentional difficulties in individuals suffering from job burnout (22). The CFQ may correctly identify actual global cognitive deficits given the comprehensive scope of the scale (14).
The current study aims were to (i) assess the concurrent validity of the SCIP-D and the CFQ through associations with neuropsychological functioning in a sample of patients with work-related stress complaints, (ii) determine the optimal cut-off scores on the SCIP-D and on the CFQ for prediction of objective cognitive impairment quantified by a battery of standardized neuropsychological tests, (iii) assess the sensitivity of the SCIP-D to cognitive impairment in patients with workrelated stress through comparisons with HC, and (iv) investigate the equivalence of the three parallel versions of the SCIP-D within the patient sample.

Methods

Patients and procedures

This cross-sectional study included adult outpatients with work-related stress (ICD-10 codes F43.2; F43.9; Z56) recruited consecutively from March 2019 through February 2020 in the Stress Reduction Clinic at the Department of Occupational and Environmental Medicine, Bispebjerg Hospital. The inclusion criteria for the patients comprised 18-64 years of age, significant workrelated exhaustion symptoms (Karolínska Exhaustion Disorder Scale, 9-item, [KEDS]: total scores >20) (23, 24), and native Danish language. The exclusion criteria were dyslexia, alcohol or substance abuse, substantial somatic illness, somatic illness or disability known to cause cognitive impairment, personal history of clinical depression, and current psychiatric illness; however, we allowed for mild depressive symptoms defined as Hamilton Depression Rating Scale, 6-item, (HDRS-6) (25) scores <8.
Initially, patients referred to the department for examination of work-related stress were screened for study eligibility by medical doctors. For research purposes, eligible patients attended a single 1.5-hour session in the clinic administered by the first author for obtaining background information, assessment of neuropsychological functioning, completion of self-reported cognitive impairment, and rating of depressive symptoms.
All participants provided informed written consent and were offered a small gift card certificate for their study participation. According to the local ethics committee, ethical approval was not required as the study did not involve biomedical or invasive procedures. The study complies with the Helsinki Declaration of 1964 and its later amendments.

Background information

Patients' data on background information included age, sex, years of education, premorbid verbal intelligence [Danish Adult Reading Test (DART)] (26, 27), occupational status, marital status, number of days sick-listed, and number of previous work-related stress episodes, depressive symptoms (25), non-restorative sleep (28), and perceived stress (29, 30). Patients without sleeping disturbances per se (eg, sleep onset, interruptions) may still feel unrefreshed upon awakening. Non-restorative sleep within the past seven days was assessed by the 9-item Restorative Sleep Questionnaire Weekly Version (RSQW) using a five-point Likert scale (ranging from 1="Not at all" to 5="Completely") (supplementary material, www.sjweh.fi/article/3990, item 1) with lower scores indicating a worse non-restorative sleep. The scale was computed by the following formula (28):

RSQW Total Score = {RSQW average score across completed items - 1} ·25

Premorbid verbal intelligence was estimated by the following formula (26):

Premorbid verbal intelligence = 128 - (0.83 ·number of DART errors)

Objective measures of cognitive status

All patients were assessed with SCIP-D form 3, while the SCIP-D forms 1 and 2 were administered alternately between patients by the end of each session. The SCIP-D has five subtests and the instrument is feasible to administer (<20 minutes) by trained staff for assessment of verbal learning and memory (VLT-I), delayed memory (VLT-D), working memory (WMT), verbal fluency (VFT), and processing speed (PST). For administration details see (15). Each SCIP-D subtest was scored by summing correct responses to that test (eg, no correct responses would score 0, which is the lowest score possible). The SCIP-D total-score index of global cognitive functioning was computed by summing the raw scores of all five subtests. The VFT (and hence the SCIP-D total score) has no upper limit score.

Consistent with previous studies validating the SCIP-D (18, 19), we matched the five SCIP-D subtests to corresponding standardized neuropsychological tests tapping into the same cognitive domains: Rey Auditory Verbal Learning Test (RAVLT) total recall across the five learning trials (I-V) (31) (SCIP-D: VLT-I), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Span Forward (32), the WAIS-III Letter-Number Sequencing (33) (SCIP-D: WMT), verbal fluency tests with the letters S and D (34) (SCIP-D: VFT), RAVLT recall following interference and 30 min. delay (SCIP-D: VLT-D), and the Trail Making Test part A (35) (SCIP-D: PST). Multiple neuropsychological tests were matched to reflect the cognitive functions assessed by the SCIP-D total score and subtests for WMT and VLT-D, respectively (table 1).

Healthy control (HC) sample

A patient-matched HC sample was created to establish robust thresholds for identification of cognitive impairment (yes/no). We used bootstrapping with 1000 repeatedly samplings to match a pre-existing data pool of HC (N=103) (19) to the patient sample (N=82) according to stratas of sex, age, verbal intelligence (tertiles) (36). This technique matches each patient to 1000 randomly drawn HC (with replacement) from the data pool having the same combination of stratas (eg, middle-aged female with a high premorbid intelligence). This implies that the same individual HC could be matched to multiple patients and that multiple HC could be matched to the same individual patient. We chose this approach to introduce novel norm variation, because the HC were recruited for a previous study validating the SCIP-D in psychiatric populations (18, 19).

The 103 HC were recruited in the blood bank at Copenhagen University Hospital, Rigshospitalet from January 2014 to June 2015 and assessed with identical tests administered in the same order as the current patients. Background information of the HC included age, sex, verbal intelligence (26, 27), perceived stress (29, 30), and the Hamilton Depression Rating Scale, 17-item version (25). For details see (19). In this study, we applied an additional HC exclusion criterion of excess perceived stress defined as a score of >20 on the Perceived Stress Scale corresponding to >1 SD above the general population mean (29, 30).

Normative objective cognitive functioning

All neuropsychological test scores of the patients were z-score standardized to the matched HC sample (mean 0, SD 1) allowing immediate comparison with normative scores. The z-scores for Trail Making Test part A were inversed to adjust for negative proportionality. The mean composite scores were computed by averaging the z-

scores of the subscales (table 1).

Subjective measure of cognitive status

Subjective cognitive functioning was assessed by the 25-item Cognitive Failure Questionnaire (CFQ) using a five-point Likert scale (ranging from 0="Never" to 4-'Very often") (20). The CFQ total score was computed by summing the rating scores for all 25 items (scale: 0-100). A higher CFQ total score indicates more lapses of attention, perception and memory in daily life, eg, losing task goals during execution and forgetting names more often (21). The CFQ total score was matched to the mean composite measure for global cognitive functioning to tap into the same cognitive domains (table 1). There were no CFQ norm data in the matched HC sample.

Statistical analyses

All statistical analyses were performed using SAS Studio version 3.8 (SAS Institute, Cary, NC, USA) on a logged server hosted by the Capital Region of Denmark. The general alpha level of statistical significance was set to 0.05 unless otherwise stated.

The concurrent validity of all SCIP-D scores and the CFQ total score (aim i) was assessed using Pearson's correlation coefficient according to their matched standardized neuropsychological measure. As a sensitivity analysis, we examined the adjusted association between objective and subjective measures of cognitive status using linear regression to evaluate the potential bias from covariation by age, sex, years of education, premorbid verbal intelligence, occupational status, marital status, days sick-listed, previous episodes, depressive symptoms, non-restorative sleep, and perceived stress.

We determined the clinical applicability of SCIPD D CFQ for correctly discriminating between true cases/non-cases of objective cognitive impairment (aim ii). This was conducted using logistic receiver-operating-characteristic (ROC) regression analyses for all SCIP-D scores and the CFQ total score according to objective cognitive impairment classified by each of their matched neuropsychological measures (yes/no) (37). Adding to the clinical applicability of the results, we computed a conservative and a relaxed set of thresholds indicating objective cognitive impairment: the conservative thresholds were 1.5 SD and 2.0 SD below the HC mean z-scores for global and focal cognitive impairment, respectively, while the relaxed thresholds were 1.0 SD and 1.5 SD below each of the same HC measures of cognition, respectively.

We compared differences in SCIP-D total scores and subtest scores between patients and HC (aim iii) using independent t-test (two-tailed). Cohen's d values were calculated to determine the effect sizes. For differences in the five SCIP-D subtest scores, the threshold for statistical significance was set to an alpha level of 0.01 to adjust for multiple comparisons.

Finally, we assessed concurrent validity of the SCIPD D 1-3 (aim iv) by analyzing Person's correlation coefficients between the total scores of all three parallel SCIP-D versions and the standardized measure of global cognitive functioning.

Results

A total of 369 patients were referred to the clinic of whom 110 were eligible for this study. Of these, 28 patients were excluded for the following reasons: no wish to participate (N=10), no response to attempted contact via telephone (N=12), displayed excess depressive symptoms (N=4), and other reasons (N=2). Consequently, 82 patients attended a 1.5-hour assessment session defining the patient sample (supplementary material 2). Of these, 12 patients did not complete one of the alternated SCIP-D forms 1-2 due to excess fatigue ending the assessment session.

In the bootstrapping procedure for establishment of the matched HC sample, we excluded four female patients due to missing data or no available HC match according to the three matching variables. We excluded one HC from the total data pool due to excess perceived stress. Thus, we were able to match a total 78 patients to randomly drawn data from 79 individual HC. Finally, the matched HC sample included 78 000 HC observations as we selected 1000 bootstrapping resamples to the 78 patients eligible for matching (table 2). We assigned the HC norms scores to the full patient sample (N=82).

Table 3 presents the characteristics of the patient sample and the matched HC sample (N=78 000). The patient and

HC samples were comparable regarding the sex composition, years of age, and estimated verbal intelligence. On average, the patients performed -0.9 SD lower than the HC mean on the global composite score of the standardized neuropsychological tests. The patients rated an average CFQ total score of 52.0 (SD 11.7). Supplementary material 3 presents raw scores of the measures for objective cognitive status.

Concurrent validity (aim i)

We found that all SCIP-D scores were correlated with their matched standardized measure of cognitive functioning (SCIP-D total score: r=0.76, subtest scores: r=0.40-0.70, P<0.001). The CFQ total score was neither associated with the SCIP-D total score (r=-0.01, P=0.96) nor the standardized measure of global cognitive functioning (r=-0.12, P=0.30). Based on visual inspection of scatterplots and Q-Q-plots, correlation coefficients were unsusceptible to bias from outliers or non-linear associations (data not shown). The finding of no correlation between objective and subjective measures of cognitive status was supported when adjusting for covariation by age, sex, years of education, premorbid verbal intelligence, occupational status, marital status, days sick-listed, previous episodes, depressive symptoms, non-restorative sleep, and perceived stress (unadjusted model: betaCFQ Total Score=-0.02, P=0.30 versus the adjusted model: betaCFQ Total Score>-0.001, P=0.80).

Optimal cut-offs (aim ii)

Table 4 presents the proposed cut-off values for the SCIP-D total and subtest scores to identify patients as "cognitively impaired" based on conservative (ie, 1.5 SD and 2.0 SD below the HC mean for global and focal cognitive impairment, respectively) and more relaxed impairment thresholds (ie, 1.0 SD and 1.5 SD, respectively). The proposed conservative SCIP-D total-score cut-off of <72 classified 43.2% of the patients with cognitive impairment compared to 28.6% of the HC (sensitivity: 0.77, specificity: 0.73). The proposed CFQ cut-off value of >54 yielded lower values of sensitivity (0.52) and specificity (0.63), suggesting a poor clinical applicability of the self-assessed CFQ for detection of objective cognitive impairment.

Sensitivity of the SCIP-D to cognitive impairment in patients with work-related stress (aim iii)

On the SCIP-D, the patients scored significantly lower on the total score and the subtests for working memory (Cohen's d-values=0.39) and visuomotor processing speed (d=0.61) compared to the HC (table 5). We found no differences in the severity of cognitive complaints among patients identified with and without cognitive impairment according to the conservative SCIP-D totalscore cut of <72 (mean 52.1, SD 12.5 and mean 51.9, SD 11.3, respectively, t(78)=-0.06, P=0.95).

Equivalence of the SCIP-D versions (aim iv)

Total scores of the SCIP-D form 3 and the standardized measure of global cognitive functioning were highly correlated with total scores of SCIP-D forms 1 (N=35) and 2 (N=34) (r>0.65, P<0.001).

Discussion

We evaluated objective (performance-based) and subjective (self-report) tools for screening of neurocognitive impairment among patients with work-related stress. Associations with comprehensive neuropsychological tests indicated good concurrent validity of the objective cognitive screener, SCIP-D, but not the subjective tool, CFQ. The SCIP-D showed superior decision validity to the CFQ using a cut-score approach for correct classification of patients with objective cognitive impairment. Specifically, the two SCIP-D subtests for working memory and processing speed were particularly sensitive, while the SCIP-D subtests for verbal fluency, learning and memory recall were not statistically different between patients and HC. The equivalence of the three parallel versions of the SCIP-D among patients was indicated.

Corroborating earlier studies, we found no significant association between objective and subjective measures of cognition (8, 12-14, 18, 19). This finding prevailed when adjusting for potential covariates, suggesting that the lack of association was not attributable to bias by confounding, such as depressive symptoms, consistent with previous results (12). As demonstrated in affective disorders, the SCIP-D yielded valid psychometric properties for screening of objective cognitive impairment among patients with work-related stress (18, 19).

A conservative SCIP-D total-score cut of <72 yielded marginally lower sensitivity and specificity values among patients than a more relaxed cut of <75 did. However, the conservative SCIP-D total-score cut classified 28.6% of

HC as cognitively impaired, while this number was 40.6% for the relaxed cut, suggesting an excess false-positive rate in the present HC sample. We identified about half of the patients with mild-to-moderate global objective impairment in line with previous findings among comparable (3, 9) and psychiatric populations (18, 19). Particularly, the present patients displayed lower performance on the subtests for processing speed (Cohen's d=0.61) and working memory (d=0.39) (38) comparable to point d-estimates of similar patients recruited in another Danish department of occupational medicine (d=0.69, P<0.01 and d=0.28, P=0.13, respectively) (5). We observed no significantly impaired performance on the remaining subtests, although the scores for immediate verbal learning indicated mild memory dysfunctions relative to the HC (P=0.02). This should not be taken as strong evidence for the non-existence of impairments in verbal fluency and delayed recall in this patient group, as prior studies have reported impaired performance in these cognitive functions (8-10, 39). Patients identified with and without global cognitive impairment on the SCIP-D reported similar levels of subjective cognitive impairment, supporting that performance-based and self-report cognitive deficits are uncorrelated features in patients with work-related stress. The concurrent validity of the parallel SCIP-D forms is in keeping with previous findings (18, 19), suggesting that the three versions could be administered for tracking of cognitive status. Yet, more studies using a randomized administration order in work-related stress are needed to support such applicability of the SCIP-D.

The patients' average CFQ total score for subjective cognitive impairment concurred with previous findings (mean 54.4, SD 14.1) (2). We had no HC data available on the CFQ measure in the present study. However, according to another similarly composed HC sample with normative CFQ data (mean 24.9, SD 10.8) (2), 82.7% of the current patients can be identified with global subjective cognitive impairment according to a conservative cut-off (ie, CFQ total score >41). This suggests that the prevalence of subjective cognitive impairment is higher than objective cognitive impairment in work-related stress and that self-assessment of cognitive status cannot replace objective performance testing of cognitive skills. Moreover, we determined the same optimal CFQ total-score cut with unsatisfactory area-under-curve values according to both impairment thresholds, reflecting the poor decision validity of the CFQ for detection of performance-based cognitive deficits.

In line with recommendations from psychiatry (18, 19), we propose that cognitive impairment is evaluated with a brief objective cognitive screener in addition to subjective cognitive difficulties among patients with work-related stress. If using the SCIP-D for this purpose, we recommend applying the proposed conservative thresholds for cognitive impairment (eg, SCIP-D total score <72), since the present results suggested a higher false-positive rate - at least among the HC sample. In addition, we advocate that the SCIP-D cut scores are interpreted in accordance with clinical judgement to individually account for premorbid factors linked to cognitive functioning, eg, age, years of education, estimated premorbid intelligence (40). The brevity of the SCIP-D for feasible screening of impairment is a trade-off for a more in-depth insight into neurocognitive functioning. Therefore, the SCIP-D should only be administered for screening purposes and not replace a full-scale neurocognitive examination.

Ellbin et al (8) previously validated the Swedish version of the Cognitive Assessment Battery as an objective cognitive screener in stress-related exhaustion. The CAB comprises six subtests assessing similar cognitive domains as the SCIP-D, although the CAB has no measure for global cognitive status. To our knowledge, the CAB only exists in one form poorly applicable to longitudinal monitoring of cognitive status due to learning bias.

The current study has some limitations. The proportion of patients identified with cognitive impairments may be underestimated due to few severely affected patients in the sample. Patients with greater exhaustion symptoms and/or cognitive impairment may lack the vigor and motivation to volunteer for a demanding assessment session. More severely affected patients may display greater subsidiary depressive symptoms of HDRS-6 scores >8, which was an exclusion criterion for study participation. The HC sample size was insufficient to calculate demographically adjusted norm cut-offs for cognitive impairment (40) in contrast to a more simple "one-cut" approach based on average scores in the present study. The normative sample was established based on a data pool of HC recruited in a previous study (18, 19), which potentially replicates systematic error, if any. This source of error was reduced as we matched eligible HC using a bootstrapping technique that introduced unique variation in normative cognitive functioning. Finally, the present study did not include a measure of insufficient effort (eg, Test of Memory

Malingering, [TOMM]) (41). It is possible that some test takers may intentionally underperform, though this seems unlikely as participation was voluntary. Our clinical experience is that the vast majority of occupational patients with prolonged work-related stress wish to resume their normal work life.

Strengths of the study were the large patient sample (N=82) matched with data from 79 individual HC, providing statistical power to evaluate the study aims. It was also a strength that we validated a feasible objec-tive cognitive screener with parallel forms that can be implemented in occupational clinics and research for administration by non-specialist healthcare providers with some experience in assessment. Specifically, in addition to subtest scores for five typically affected cognitive functions, the SCIP-D offers a total score that is easy to interpret and evaluate. Administration of the SCIP-D is brief, which does not fatigue the patients as much as a conventional neurocognitive examination.

Concluding remarks

In this study, patients with work-related stress showed impaired performance on tests for global cognitive functioning, particularly processing speed and working memory, while objective and subjective measures of cognitive status were poorly correlated. The objective cognitive screener, SCIP-D, was a valid and feasible tool to identify and monitor objective cognitive impairment using a cut-off score in this patient group. Based on these findings, we recommend screening for objective cognitive impairment using the Danish SCIP-D evaluated according to the conservative cut-off scores and clinical judgment among patients with work-related stress, who complain about cognitive difficulties.

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Please contact Professor Scot E. Purdon [spurdon@ ualberta.ca] for permission to use the Screen for Cognitive Impairment in Psychiatry (SCIP).

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Conflict of interest

KWM declares having received consultancy fees from Lundbeck and Janssen in the past three years. SEP receives royalties and/or licensing fees from commercial applications of the English and the Spanish language forms of the Screen for Cognitive Impairment in Psychiatry. JHJ, JFT, and NHE declare no potential conflict of interest.

Sidebar

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DETAILS

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Job strain and effort-reward imbalance as risk factors for type 2 diabetes mellitus: A systematic review and meta-analysis of prospective studies

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ABSTRACT (ENGLISH)

Objectives This systematic review and meta-analysis aimed to synthesize the available data on prospective associations between work-related stressors and the risk of type 2 diabetes mellitus (T2DM) among adult workers, according to the demand-control-support (DCS) and the effort-reward imbalance (ERI) models. Method We searched for prospective studies in PubMed, EMBASE, Web of Science, Scopus, CINHAL and PsychInfo. After screening and extraction, quality of evidence was assessed using the ROBINS-I tool adapted for observational studies. The effect estimates extracted for each cohort were synthesized using random effect models. Results We included 18 studies (reporting data on 25 cohorts) in meta-analyses for job strain, job demands, job control, social support at work and ERI. Workers exposed to job strain had a higher risk of developing T2DM when compared to unexposed workers [pooled rate ratio (RR) 1.16, 95% confidence interval (CI) 1.07-1.26]. This association was robust in several supplementary analyses. For exposed women relative to unexposed women, the RR was 1.35 (95% CI 1.12-1.64). The RR of workers exposed to ERI was 1.24 (95% CI 1.08-1.42) compared to unexposed workers. Conclusions This is the first meta-analysis to find an effect of ERI on the onset of T2DM incidence. It also confirms that job strain increases the incidence of T2DM, especially among women.

FULL TEXT

Headnote

Objectives This systematic review and meta-analysis aimed to synthesize the available data on prospective associations between work-related stressors and the risk of type 2 diabetes mellitus (T2DM) among adult workers, according to the demand-control-support (DCS) and the effort-reward imbalance (ERI) models. Method We searched for prospective studies in PubMed, EMBASE, Web of Science, Scopus, CINHAL and PsychInfo. After screening and extraction, quality of evidence was assessed using the ROBINS-I tool adapted for observational studies. The effect estimates extracted for each cohort were synthesized using random effect models. Results We included 18 studies (reporting data on 25 cohorts) in meta-analyses for job strain, job demands, job control, social support at work and ERI. Workers exposed to job strain had a higher risk of developing T2DM when compared to unexposed workers [pooled rate ratio (RR) 1.16, 95% confidence interval (CI) 1.07-1.26]. This association was robust in several supplementary analyses. For exposed women relative to unexposed women, the RR was 1.35 (95% CI 1.12-1.64). The RR of workers exposed to ERI was 1.24 (95% CI 1.08-1.42) compared to unexposed workers. Conclusions This is the first meta-analysis to find an effect of ERI on the onset of T2DM incidence. It also confirms that job strain increases the incidence of T2DM, especially among women.

Key terms adult-onset diabetes; cohort study; demand-control; ERI; ROBINS-I; work stress.

Type 2 diabetes mellitus (T2DM) is a rapidly growing health problem worldwide. The World Health Organization estimates that from 1980 to 2014, worldwide T2DM prevalence among adults rose from 4.7% to 8.5% (1).

Despite an overall increase in life expectancy over the past decades, disability-adjusted life expectancy has not kept up with this gain. Among the elderly, for example, death is often preceded by years of chronic disease (2). In this regard, T2DM currently occupies fourth place among the conditions that most strongly reduce disability-adjusted life years (2).

With the aim of reducing worldwide mortality from chronic diseases by 25% by 2025, the World Health Organization published the 25x25 Global Action Plan (3) which proposes to prevent the increase in the prevalence of T2DM

through changes in dietary patterns and physical activity. However, in addition to other major guidelines (4, 5), that plan does not discuss the importance of factors related to the work environment. With the rapid aging of the population, countries in Europe and North America are putting in place incentives for later retirement (6, 7). The population is therefore exposed for a longer period to the work environment, including work-related stressors, and it becomes even more important to consider these as risk factors for chronic diseases.

Work-related stressors are most frequently measured by the demand-control-support (DCS) and effort-reward imbalance (ERI) models. In the DCS model, the combination of high psychosocial demands and low job control, defined as job strain, is the most harmful to health (8). The ERI model assumes that effort at work is spent as part of a contract based on the norm of social reciprocity, where rewards are provided in terms of money, esteem, and career opportunities including job security. It proposes that risks to health arise from a perceived breach of this contract. The perception of this imbalance is affected by personal coping characteristics (overcommitment) (9).

A body of evidence built in recent decades from longitudinal studies in large cohorts of workers has found that work-related stressors, defined according to either of these models, are associated with a moderately higher risk of cardiovascular disease and stroke (10). However, the association between work-related stressors and T2DM remains uncertain: while some studies have found a positive association (11), others have not (12, 13).

The two previous meta-analyses on prospective studies measured work-related stressors only according to the DCS model (14, 15). The most recent meta-analysis differs from the previous one with its inclusion of only one additional study (16). Including this extra study led to observing a significant effect of job strain on T2DM incidence [relative risk 1.16, 95% confidence interval (CI) 1.03-1.31], while the previous meta-analysis had not seen a significant effect (relative risk 1.12, 95% CI 0.95-1.32). This instability casts doubt on the robustness of the findings and warrants further investigation. It is noteworthy that both these meta-analyses are strongly driven by a single aggregated cohort study (11), further decreasing the robustness of the findings.

Here, we have evaluated the risk of bias separately for each cohort using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (17) adapted for occupational studies (18). The separate evaluation avoids giving any single published study too much weight and avoids counting the same participants more than once when they appear in several published studies.

Furthermore, we included original studies published very recently that have not yet been incorporated into any previous reviews (13, 19, 20). Specifically, enough studies have now been published using the ERI model that we are able to present the first meta-analysis using this model.

Methods

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (21) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines (22).

Inclusion and exclusion criteria

Eligibility criteria. Studies were eligible if they were (i) published after 1979 [the date of the first publication using the oldest validated theoretical model considered in this systematic review (DCS)] (23); (ii) measured the exposure using at least one of the two work-related stressor models considered, and (iii) measured the incidence of T2DM.

Population

The target population of this systematic review included all adult male and female workers. To avoid reverse causality bias, studies involving only sick participants were not considered. Furthermore, studies on pregnant women were excluded because of pregnancy-related traits that may confound the association between workrelated stressors and T2DM.

Exposure

All dimensions of the DCS or ERI models were considered: psychological work demands, job control, social support (from colleagues and/or supervisors) as well as efforts, rewards at work and overcommitment. Combinations of these dimensions were also considered: job strain (high psychological demands combined with low control), iso-strain (job strain combined with low social support) and ERI (ratio between efforts and rewards).

Comparator

The comparison group had to be from the same study population and a group of workers exposed to the lowest category of the work-related stressors mentioned above.

Outcomes

The types of incident T2DM considered included clinical measurements [blood glucose, blood insulin, glycated hemoglobin or Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)]; physician-certified or from administrative data (physician services or medication); and self-reported.

Study design

To avoid the possibility of introducing recall bias and reverse causality, only original studies with prospective design were considered, specifically cohort and nested case-control studies. There was no restriction on the minimum follow-up time.

Data sources and search strategy

The first author identified articles on 14-20 February 2019 through PubMed (NCBI), EMBASE, PsycINFO (Ovid), Web of Science, CINAHL (EBSCOhost), and Scopus (Elsevier). On 12-14 April 2021, the searches were updated for PubMed and Web of Science. The reference lists of all eligible studies were also consulted.

For each database, five sets of keywords were used referring to (i) population (workers); (ii) exposure (fac-tors of the DCS and ERI models); (iii) concepts and terms that refer to both population and exposure (eg, "work stress"); (iv) outcome (synonyms for T2DM); and (v) prospective study design. The original search was not restricted by date of publication, language nor country of origin. The complete search strategy is avail-able in the supplementary material, https://www.sjweh. fi/article/3987, table S1.

Selection process

As a pilot, two researchers independently reviewed papers published only between 2014 and 2019. Comparison of divergences was used to clarify eligibility criteria. Using these criteria, titles and abstracts of all papers were evaluated for potential relevance. At this stage, a concordance rate (Cohen's kappa coefficient) of 0.713 between two reviewers was calculated. Then, each of the reviewers read the full text of any publication considered by either of them to be "relevant" or "potentially relevant" based on titles and abstracts. When articles could not be accessed, efforts were made to obtain them through the Laval University library or by contacting the authors directly. During full-text screening, potentially relevant articles were read in English, Portuguese, Spanish, German or French. A final consensus decision on inclusion was made based on the full text.

Data collection and evaluation of risk of bias

To maintain homogeneity and reliability of data extraction, a codebook with definitions of the values to be extracted was constructed. Numeric values and comments on the study population and design, the definition and prevalence of work-related stressors and of T2DM, the type of analysist - including the covariates used - and estimates of the effect measures [odds ratio (OR) or hazard ratio (HR)] with 95% confidence intervals (CI) were extracted from each eligible study by two trained and independent reviewers (table 1).

To assess the strength of the evidence for each study, we applied the ROBINS-I tool (17), recently adapted by Duchaine et al (18) for prospective occupational observational studies (supplementary text 1). For each study, two independent and blinded reviewers evaluated five bias domains: (i) confounding, (ii) selection of participants into the study, (iii) classification of interventions, (iv) missing data, and (v) measurement of outcomes. In each domain, the risk of bias was graded as "low", "moderate", "serious" or "critical". However, following the adapted ROBINS-I tool, the risks of confounding bias and bias for selection at study entry were never considered low (18).

Studies that used clinical criteria for diagnosing T2DM that deviated from the official American Association for Diabetes or World Health Organization guidelines (4, 24) were considered to have a critical risk of bias in measurement of outcomes.

Meta-analysis

For meta-analyses, when studies reported estimates of risk in more than one cohort, the results for each individual cohort were used. Among different risk estimates for the same exposure measure in one cohort, we gave preference to those that reported HR and those that used dichotomized exposure. On the other hand, whenever there was more

than one publication that estimated an effect from the same kind of exposure in the same cohort, we used only the one that had the highest average follow-up or the most collection waves. The estimates for job strain by quadrants published in a note by Kivimäki et al (25) were evaluated together with the original publication (11). For each exposure scale, the choice of the most appropriate model was made based on adjustment at least for sex, age and socio-economic status (eg, education, occupation type, income), and the absence of adjustment for possible mediating variables.

Results are shown for whole populations and male and female subjects separately. When incidence estimates were available, HR and OR were transformed to rate ratios (RR) (26), but only if this could be done for all cohorts in a given meta-analysis. In order to convert HR into RR, it was necessary to first estimate r0, the rate of incidence of diabetes among the non-exposed, from the overall rate of incidence of diabetes r, from the proportion of unexposed subjects, p0, and exposed subjects, p1, and from the HR as

r=r / p + Pi HR)

RR were then estimated as:

RR=(1-eHR * ln(1-r0)) / r0

Analogously, the cumulative incidence of cases of diabetes at the end of a study, f0, was estimated from the overall cumulative incidence, f, as

f=f/ (P0 + Pi * OR).

RR were then estimated from odds ratios (OR) as

RR=OR / (1 - f + f * OR)

For each form of exposure, we estimated its combined effect on the incidence of T2DM from the individual studies using random effects meta-analyses and assessed heterogeneity with the I2 statistic and the Cochran Q-test (t2). Supplementary analyses were done on subgroups defined by effect measure and by overall risk of bias. All calculations were performed using the R library meta (27, 28) at a significance level of $P<0.05$. Forest plots and funnel plots were generated by the same library.

Results

We found a total of 2479 potentially eligible citations, and 113 studies were retained for full text reading (supplementary figure S1). F inally, data from the 21 publications that met our criteria were extracted for systematic review (table 1), quality assessment (table 2) and meta-analysis.

Systematic review

Regarding population characteristics, almost all studies were conducted in high-income countries, with one exception (Brazil) (19). In addition to the populations of large, well-known cohorts, such as GAZEL, Whitehall II, SLOSH (11, 29), MONIKA (30), CCHS (13, 31), among others, this review also included a variety of cohorts composed of healthcare workers (12, 32, 33), police officers (34), factory workers (35), civil servants (19, 36), and workers >60 years (16). The average age of participants at baseline was 35-73 years and mean follow-up durations were 2.7-13.5 years.

Among the 21 studies included in the systematic review, 19 measured work-related stressors according to the DCS. The ERI model was included in 3 studies (19, 34, 36), while 2 defined work-related stressors exclusively according to the ERI model (20, 37). Within the DCS framework, 14 studies used categorical or continuous job strain as exposure (11-13, 16, 19, 29, 30, 32-35, 38-41), 7 used high psychosocial demands and low control (19, 31, 32, 36, 38, 42, 43) and 8 used low social support at work (19, 29, 31, 32, 36, 38, 43, 44). Iso-strain was used in 2 studies (19, 38). Within the ERI framework, all 4 studies used categorical or continuous ERI as exposure, and only 1 (19) also used overcommitment.

T2DM was defined by three types of measures: (i) diagnosed by clinical tests of fasting plasma glucose, glucose tolerance or glycosylated hemoglobin (19, 32, 34, 41, 42); (ii) health system administrative records (13, 20, 31, 33); or (iii) self-reported through questions like "Has a doctor ever told you that you have diabetes or high blood sugar?" (37, 40). Nine studies used combinations of these three measurements (11, 12, 29, 30, 36, 38, 39, 43, 45). While all studies excluded prevalent cases from analyses, in one study exclusion was based on metabolic syndrome, not

T2DM (41).

Quality assessment

We assessed the quality of evidence according to the five criteria of ROBINS-I (17). Summaries of the evaluation of each study in each domain can be found in supplementary text 2.

Regarding confounding bias, 18 out of 21 studies adjusted for the potential confounding covariables sex, age and some indicators of social status. However, only 8 studies were classified as having the lowest possible risk of confounding bias for observational studies (moderate) (11, 12, 16, 20, 29, 30, 32, 37), since the others additionally adjusted for variables that potentially mediate the association between work-related stressors and T2DM (13, 19, 31, 36, 39-44).

With respect to the selection of participants, six cohorts in five studies were considered to have a moderate risk of bias (80-100% participation rate) (11, 31, 34, 35, 43). Twenty estimates were classified at serious (54-76% participation rate) (11-13, 16, 20, 29, 30, 36, 38, 39, 41, 42) and nine at critical risk of selection bias (21-59% participation rate) (11, 19, 29, 32, 33).

With regard to work-related stressors, 11 cohorts in six studies had a low risk of exposure classification bias because they used validated instruments (11, 12, 19, 29, 30, 33), while the others used instruments that had not been validated or only partially validated.

Regarding the outcome, the cohorts in most studies had a low-to-moderate risk of bias. Four cohorts had serious risk (11, 29, 37, 40), and in three studies (32, 34, 41), there was a critical risk of misclassification: defining diabetes at a cut-off of 100 mg/dl (5.6 mmol/L) fasting plasma glucose would also include patients with pre-diabetes and insulin resistance.

Regarding missing data bias, 20 cohorts in 11 studies had a low-to-moderate risk of bias, ie, 1-20% missing data (11, 13, 16, 19, 20, 31, 33, 34, 36, 38, 42).

Altogether and according to the definition of the adapted ROBINS-I tool (table 2), for 2 of the 35 published estimates, the highest risk of bias in any domain was moderate and for 20, it was serious. For the other 13 estimates, the highest risk was critical.

Results of meta-analyses for job strain

Altogether, 28 cohorts from 21 studies met our inclusion criteria. Meta-analyses were performed whenever there were at least three independent risk estimates for the same type of exposure measure; therefore, 25 cohorts from 18 studies were used in meta-analyses. For job strain, we used the individual estimates from each of the 15 cohorts that had no critical risk of bias in any domain (figure 1A). Estimates published by Heraclides et al (38), Heraclides et al (39) and Mortensen et al (29) refer to populations also reported by Nyberg et al (11), but with shorter follow-up durations. They were therefore disregarded. According to the summary estimate, workers exposed to job strain had a higher risk of T2DM compared to non-exposed workers: RR 1.16 (95% CI 1.07-1.26). There was no evidence of heterogeneity between studies (I2=0%, t2=0; P=0.88). The funnel plot shows no outlier studies (figure 2), and there is no statistical evidence for a publication bias in this set (P=0.27).

In subgroup analyses (figure 1B-C), women exposed to job strain had a higher pooled estimate (RR 1.35), but, due to the smaller number of studies (12, 13, 19, 33, 39, 42), the CI included most of the estimate range for the total population (95% CI 1.12-1.64). There was low heterogeneity (I2=13%, t2 <0.01; P=0.33). For men, there was a tendency towards an apparent protective effect of job strain against T2DM incidence [RR 0.84 (95% CI 0.70-1.01), I2=11%, t2 <0.01, P=0.35], but this tendency disappeared in supplementary analyses (see Section 3.5). When comparing only results from those cohorts that published results for both sexes separately (13, 19, 33, 39, 42), the difference between the effects in the strata of sex was significant (x2=15.12, df=1, P<0.01).

High psychosocial demands, low control and low social support at work were not significantly associated with the incidence of T2DM in the whole population nor in strata of sex (supplementary figure S2-4). However, job control showed a tendency towards a protective effect against T2DM in men (supplementary figure S3B).

Results of meta-analyses for ERI

All analyses up this point refer to the DCS model, which has been the subject of previous meta-analyses. Pooled

effects for the other major model for work-related stressors, the ERI model, had not yet been estimated because there were not enough original studies available. Our analysis of four studies, including two very recent ones (figure 3) (19, 20, 36, 37) indicates a significant pooled effect [RR 1.24 (95% CI 1.08-1.42); I2=0%, t2 <0.01, P=0.75]. These estimates are based on categorical definitions of ERI (table 1). There are not yet enough sex-specific estimates for categorical ERI to allow subgroup analyses.

Supplementary analyses

We performed a supplementary meta-analysis for all 22 cohorts that analyzed the effect of job strain, irrespective of their risk of bias, and using the published HR and OR values without transformation (supplementary figure S5). The estimate was very similar to the main analysis [relative risk 1.17 (95% CI 1.09-1.25); I2=0%; t2 <0.01, P=0.79].

We also repeated this analysis using the pooled estimate previously published by Nyberg et al (supplementary figure S6). The point estimate and CI are slightly higher than in our main analysis [RR 1.19 (95% CI 1.07-1.33)], but there was evidence of moderate heterogeneity (I2=22%; t2 <0.01, P=0.23) and of possible publication bias in this supplementary analysis (supplementary figure S7). The effects estimated separately for women [RR 1.26 (95% CI 1.05-1.51); I2=32%; t2=0.01, P=0.20] and men [RR 0.97 (95% CI 0.75-1.25); I2=55%; t2=0.05, P=0.05] broadly maintained the same relation as observed in the main analysis, but suffered from higher heterogeneity.

In all analyses up to this point, we combined studies that defined job strain as a continuous variable, as a dichotomous variable (job strain versus no strain) or as job strain quadrants (high strain versus low strain). In another supplementary analysis, we separated these study groups. For dichotomous exposure, we estimated RR 1.16 (95% CI 1.07-1.26; I2=0%; t2=0%, P= 1.00). In the case of job strain quadrants, we estimated RR 1.21 (95% CI 1.02-1.43; I2=40%; t2=0.02, P=0.12). The only study using continuous job strain reported RR 1.06 (95% CI 0.85-1.33).

As a final supplementary meta-analysis for the effect of ERI, we used the published HR and OR values without transformation (supplementary figure S8). Here also, the estimate was very similar to the main analysis [relative risk 1.24 (95% CI 1.08-1.43); I2=0%; t2=0, P=0.75].

Discussion

The main objective of this systematic review and metaanalysis, which includes 21 prospective studies with 334 132 workers and 10 806 cases of T2DM, was to synthesize the evidence regarding effects of work-related stressors (job strain and ERI) on the incidence of T2DM.

Demand-control model

Job strain was significantly associated with the risk of developing T2DM. The risk of diabetes was 16% higher among workers exposed to job strain when compared to unexposed workers, and the magnitude and significance of this relative risk were preserved in several supplementary analyses.

Among women exposed to job strain, the risk of developing T2DM was 35% higher when compared to unexposed women, which is a significantly stronger effect than among men. The absence of an association in men might be explained by pathophysiological characteristics that make men more vulnerable to the incidence of T2DM and may eclipse the effect of work stressors. In fact, a somewhat higher overall incidence in men has been reported in the literature (46, 47), and is also present in those studies in our meta-analysis that reported cumulative incidence separately for men (6.2%) and women (4.5%). As examples of pathophysiological characteristics, men have a higher turnover of fatty acids, the accumulation of visceral adipose tissue is higher among them, and it is a risk factor for T2DM independent of total BMI (46).

Another explanation would be that men are more often employed for strenuous work than women. The protection afforded by the physical exercise involved in such jobs might overcome the higher risk of T2DM expected from high psychosocial stressors (48). Such an effect might explain the tendencies towards an inversion of the association with T2DM that we observed for both job strain and job control

Not all groups have published sex-specific effect estimates for job strain, and only a very reduced number of studies have done so for job control. To understand the direction and magnitude of associations in men and women, we suggest that the analyses of work-related psychosocial stressors, including their dimensions, that are shown here be

published also stratified by sex, and we extend this suggestion to future publications.
The two most recent meta-analyses (14, 15) come to different conclusions with regard to the significance of job strain for T2DM in the total population; both of them are strongly driven by a single aggregated cohort study (11). In addition to including two recent studies (13, 19), we have here detected varying levels of risk bias among the cohorts reported in combined studies, namely those of Nyberg et al (11) and Mortensen et al (29). While our final results for job strain closely agree with those of Li et al (14), the present analysis is built on a separate evaluation of risk of bias for each cohort and avoids combined estimates; such estimates would count participants from separately published studies more than once (29, 38, 39).
Based on the few studies that evaluated high psychological demands, low control or social support, we found no significant association between any of these dimensions taken alone and the incidence of T2DM.
Effort-reward imbalance model
The present meta-analysis is the first one to estimate the contribution of work-related stressors, as defined by the ERI model, to the risk of T2DM. Based on four studies, workers experiencing ERI have a 24% higher risk of developing T2DM than unexposed workers. When restricted to categorical definitions of ERI, only two of the studies published sex-specific effect estimates, one of which observed a tendency for a stronger effect in women (19), similar to the pooled effects we have described above for job strain, while the other one found a stronger effect in men (36). We note that a third study, using a continuous definition of ERI, found almost identical effects for men and for women (20).
Limitations
In spite of our stringent evaluation of quality, it is necessary to consider possible remaining sources of bias. First, a confounding bias due to the presence of unmeasured factors associated both with T2DM and with work-related stressors might lead to an overestimation of the true effect. For example, poor general health may, on the one hand, induce a negative perception of the work environment and, on the other hand, increase the risk of T2DM by inducing lack of self-care and the adoption of unhealthy habits. Unmeasured symptoms of a pre-clinical diabetic state might induce a similar negative perception. However, pre-clinical diabetes develops almost imperceptibly (1), and one would therefore not expect it to impact psychosocial work stressors. In fact, if the studies had excluded or controlled for lifestyle habits, general health or pre-clinical T2DM, they might block a causal path and underestimate the total causal effects. Therefore, while all estimates included in our main analysis were adjusted for an indicator of socioeconomic status in addition to age and sex, reducing a possible confounding bias, we avoided estimates that had been adjusted for potential mediators.
Differential misclassification might also theoretically lead to overestimation of the true effect if self-reported T2DM was skewed by the stressors that the participant suffers at work. However, the cohorts included in the main job strain analysis used self-report data only in combination with clinical tests. We also consider the risk of differential misclassification of work-related stressors to be low, given that prevalent cases of T2DM were excluded from all cohorts.
Conversely, our estimates might underestimate the true effects. Non-differential misclassification of the outcome might be a problem since some of the included studies did not differentiate types of diabetes. However, since prevalent cases of type 1 diabetes at baseline were excluded, while the incidence of T2DM in adults is several orders of magnitude greater than that of type 1 (49, 50), the risk of misclassification for the outcome is quite low. The assessment of diabetes from medication reimbursement data might also misclassify some cases since some anti-diabetic medications are also used for treating other diseases. However, no study was based only on medication reimbursement data, and only one study in the main job strain analysis (figure 1A) and one in the ERI analysis (figure 3) relied in part on such data [Still Working (11) for job strain, Nordentoft et al (20) for ERI]. Therefore, it seems unlikely that the overall result of the meta-analysis would be noticeably affected.
Some studies assessed exposure using questionnaires that were not validated for the local language, with short and non-validated versions or with matrices of median scores derived from colleagues or peers of the participant. Such non-differential misclassification of exposures is expected to bias the effect estimates towards the null value.

Similarly, a healthy worker survival bias is inherent to occupational studies: workers generally have lower overall disease incidence than the general population due to the tendency for workers of ill health to be excluded from employment. Moreover, workers that are more exposed to work-related stressors may quit or change jobs in order to reduce their exposure. It is particularly difficult to exclude a healthy worker survival bias when participant characteristics were only measured at recruitment, as is the case for most of the cohorts included here. However, it would generally underestimate the true effect (51).

Finally, bias due to differential self-selection of participants at recruitment and especially to differential loss to follow-up is frequent in prospective studies. Here, evaluating the direction and magnitude of the distortion would require an in-depth knowledge of each cohort. A study has found that low initial participation rate may have a limited impact on estimates for some exposureoutcome relations (52). Among the studies included here, only one (20) has estimated the bias caused by a middling initial participation rate (54%) in the relation between work-related stressors and diabetes (53).

As such, we made the choice of having somewhat severe criteria for evaluating the risk of bias of initial participation selection bias. While we might have overestimated the true risk of bias of some studies, this procedure has mitigated the possible impact of a selection bias on our estimates.

Strengths

A major strength of this review and meta-analysis is the extensive search across six different databases to identify all publications on work-related stressors and diabetes published from 1979 to 2021. A rigorous assessment of the risk of bias was performed for each individual cohort, which resulted in low heterogeneity between the studies. This cohort-level analysis also allowed us to exclude duplicate risk estimates from the same population that had been published in different studies. Estimation was further improved by the use of RR. Finally, several supplementary analyses using the published pooled estimates, or restricted to subsets, such as studies using dichotomous job strain or job strain quadrants, provided similar estimates as in the main results.

Perspectives

Despite efforts to identify all eligible studies without geographical restriction, the main focus is on European, mainly Nordic, and North American cohorts. While this does not affect the internal validity of our results, they may not easily be generalizable to other regions.

The main target group of the studies was <60 years, but we can hypothesize that the effect of work-related stressors on the incidence of T2DM persists at older ages (16, 37, 40). If this is the case, since the overall incidence of T2DM is ~six times higher at age 70 then at age 40 (49), the absolute risk difference due to work-related stressors might rise if the same cohorts are accompanied until after retirement.

To put our results in perspective, it is worth comparing them with those of more proximal risk factors for diabetes, ie, factors that are widely recognized and included in worldwide programs for the prevention of chronic non-communicable diseases (3, 45). As an example of the effect of moderate physical activity, a meta-analysis concluded that among those participants who walked least, the incidence of T2DM was 18% (95% CI 9-26%) higher than among those who walked most (54). With regard to diet, subjects with high consumption of sweetened beverage had a 26% (95% CI 12-41%) higher incidence of T2DM (55). Among heavy smokers it was 28% (95% CI 4-58%) higher than among non-smokers (56). Considering that approximately 20% of workers are exposed to workrelated stressors with relative risks comparable to those of such lifestyle patterns, it seems to be relevant to investigate interventions in the work environment for prevention (57).

Concluding remarks

This systematic review and meta-analysis found evidence that workers exposed to job strain or ERI are at increased risk of developing T2DM, with women being at particularly high risk.

Our findings may be useful both for clinical practice and for conducting new research, considering that the onset of T2DM is estimated to occur 4-7 years before its clinical diagnosis (58, 59). Health professionals should be aware that patients, particularly women, who report stress at work may be at increased risk of T2DM. Considering these stressors in early screening may contribute to improve the prevention of T2DM among women.

Moving forward, more longitudinal research is needed to better assess the contribution of ERI on the risk of T2DM and whether it is modified by sex. We also suggest studies to better understand the mechanisms underlying the different effect sizes of job strain in men and women, and studies that estimate a potential cumulative effect of work-related stressors throughout working life and into retirement.

Conflict of interest &funding

Authors declare no conflicts of interest.

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Sidebar

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DETAILS

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An occupational exposure limit for welding fumes is urgently needed

Sjögren, B; Albin, M; Broberg, K; Gustavsson, P; Tinnerberg, H; Johanson, G

ABSTRACT (ENGLISH)

Approximately 11 million people work as welders worldwide and an additional 110 million are exposed to welding fumes at work (1). Several countries have an occupational exposure limit (OEL) for welding fumes of 5 mg/m3 (1,2) and similar OEL for respirable dust (2). Given the accumulating evidence on serious health effects from welding fumes <5 mg/m3, adequate worker protection including a more stringent health based OEL is an urgent issue. We therefore welcome that the European Commission has assigned the European Chemical Agency (ECHA) to propose an OEL for welding fumes at the EU level, pursuant to the Carcinogens and Mutagens Directive (CAD). It should be noted that welding fumes - besides having a very complex and variable composition - are process generated and do not fall under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation. In the following, we present some of the key issues when setting an OEL for welding fumes.

FULL TEXT

Headnote

Approximately 11 million people work as welders worldwide and an additional 110 million are exposed to welding fumes at work (1). Several countries have an occupational exposure limit (OEL) for welding fumes of 5 mg/m3 (1,2) and similar OEL for respirable dust (2). Given the accumulating evidence on serious health effects from welding fumes <5 mg/m3, adequate worker protection including a more stringent health based OEL is an urgent issue. We therefore welcome that the European Commission has assigned the European Chemical Agency (ECHA) to propose an OEL for welding fumes at the EU level, pursuant to the Carcinogens and Mutagens Directive (CAD). It should be noted that welding fumes - besides having a very complex and variable composition - are process generated and do not fall under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation. In the following, we present some of the key issues when setting an OEL for welding fumes.

Brief summary of health effects

The International Agency for Research on Cancer has classifed welding fumes as carcinogenic to humans (1). The evaluation supports chronic inflammation and immunosuppression rather than genotoxicity as a mechanism for welding-induced lung cancer. Meta-analyses have showed increased risks for lung cancer already after 3-20 years of exposure (3, 4).

Several epidemiological studies have shown increased risks for ischemic heart disease among welders (5), and a meta-analysis demonstrated increased risks of ischemic heart disease [risk ratio (RR) 1.09, 95% confidence interval (CI) 1.00-1.19, based on ten populations] as well as acute myocardial infarction (RR 1.69, 95% CI 1.18-2.42, based on three populations) (6). Ibfelt et al's study (7) showed an increased risk at 10-50 mg/m3-years (the lowest exposure category, levels are given as respirable fraction unless otherwise stated). This corresponds to 0.25-1.25 mg/m3 during 40 years of welding (5). Welders with a median respirable dust exposure <1 mg/m3 (5-95 percentile ranges 0.2-4.2 and 0.1-1.9 at two time points) developed increased systolic and diastolic blood pressure (8).

Two recent studies provide data on chronic obstructive pulmonary disease (COPD) in relation to welding fumes. A significantly increased prevalence of COPD was seen among Korean welders in both the median and high exposure tertile. The exposure in the median tertile was 3.4-11.7 mg/m3-years, corresponding to 0.1-0.3 mg/m3 during 40 years (9). In a population-based cohort in Sweden, exposure to welding fumes was associated with an increased incidence of COPD at a mean exposure to inhalable dust of 0.8 mg/m3 but not at a mean exposure of 0.08 mg/m3 (10).

Mild steel contains small amounts of manganese [typically <1.6%, (1)], a known neurotoxicant (11). Gliga et al (12) found a strong correlation between respirable manganese and respirable dust during mild steel welding. According to their calculations, the current EU OEL for respirable manganese of 0.05 mg/m3 corresponds to 0.8 mg/m3 welding fumes.

Welding fume exposure has been associated with asthma (13, 14), with stainless steel welding fumes as a specific risk factor. In Finland, the estimated incidence of occupational asthma among stainless steel welders was 1-2 among 1000 welders/year (15). Several epidemiological studies have shown an increased frequency of pneumonia

among welders. Welding fumes have also been associated with invasive pneumococcal disease (16). Exposure estimates associated with asthma and pneumonia are lacking.

Regarding effects on reproduction, a cohort following all single births in Sweden 1994-2012 showed that pregnant women with exposure to welding fumes (0.1-3.2 mg/m3) was associated with increased risks of pre-term birth and giving birth to children with low birth weight (17).

Conclusion

As illustrated herein, data on several types of negative health effects from welding fumes at low-to-moderate exposure levels are available, and there is an urgent need for a health-based OEL for welding fumes. This OEL should be based on a critical appraisal of all health effects of welding and take the various welding methods into account. Indeed, some countries have already introduced such OEL, eg, Denmark (0.5-1.7 mg/m3 depending on welding process and material (18) and The Netherlands (1 mg/m3 (2, 19).

A general OEL for welding fumes does not replace the need for specific OEL for components such as chromium, nickel, aluminium, lead and manganese, which may be present to a variable extent depending on welding technique and material. The combined use of a general OEL and specific OEL makes it easier to ensure safe levels for different types of welding. Moreover, setting an OEL is not enough. Additional measures include local exhaust ventilation and fresh-air respirators. Furthermore, the health risks mentioned above as well as the ventilation measures need to be clearly communicated, for example in safety data sheets added to packages of welding electrodes. Furthermore, welders over the age of 50 may be recommended to vaccinate against pneumococcal pneumonia (20).

Sidebar

Several countries have occupational exposure limits for welding fumes of 5 mg/m3. Given the accumulating evidence on serious health effects from welding fumes below this level, adequate worker protection including a more stringent health based occupational exposure limit is an urgent issue.

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DETAILS

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Cancer-related changes and low-to-moderate exposure to welding fumes: A longitudinal study

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ABSTRACT (ENGLISH)

Objective This study tested for an association between early cancer-related biomarkers and low-to-moderate exposure to fumes from welding mild steel. Methods Male, non-smoking participants from southern Sweden were recruited and examined (N=338, 171 welders and 167 controls); of these, 78 welders and 96 controls were examined on two occasions six years apart. Exposure to welding fumes was evaluated by measuring respirable dust, welding years, and cumulative exposure. DNA methylation of CpG sites within the cancer-related genes AHRR, F2RL3, and B3GNTL1 was measured by pyrosequencing and relative mitochondrial DNA copy number and telomere length were measured by qPCR in whole-blood samples. Multivariate models were used for longitudinal analysis. Results Median exposure to respirable dust was 0.7 mg/m3 at both timepoints, adjusted for use of personal protective equipment. Compared with controls, welders showed a significant decrease over time in DNA methylation of B3GNTL1 CpG1 and CpG4 [adjusted for age, body mass index, and smoking: ß=-0.66, standard error (SE)=0.28; ß=-0.48, SE=0.24, respectively]. In addition, exposure to respirable dust and cumulative exposure was associated with a decrease in methylation of F2RL3 CpG2 among all welders (adjusted ß=-0.67, SE=0.23 and ß=-0.03, SE=0.02, respectively). No significant associations were found for AHRR, mitochondrial DNA copy number, or telomere length. Conclusion Low-to-moderate exposure to welding fumes was associated with a small effect on selected early epigenetic biomarkers of cancer. The direction of the methylation pattern (lower methylation of specific CpG sites) indicates early lung cancer-related changes associated with mild steel welding.

FULL TEXT

Headnote

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Objective This study tested for an association between early cancer-related biomarkers and low-to-moderate exposure to fumes from welding mild steel.

Methods Male, non-smoking participants from southern Sweden were recruited and examined (N=338, 171 welders and 167 controls); of these, 78 welders and 96 controls were examined on two occasions six years apart. Exposure to welding fumes was evaluated by measuring respirable dust, welding years, and cumulative exposure. DNA methylation of CpG sites within the cancer-related genes AHRR, F2RL3, and B3GNTL1 was measured by pyrosequencing and relative mitochondrial DNA copy number and telomere length were measured by qPCR in whole-blood samples. Multivariate models were used for longitudinal analysis.

Results Median exposure to respirable dust was 0.7 mg/m3 at both timepoints, adjusted for use of personal protective equipment. Compared with controls, welders showed a significant decrease over time in DNA methylation of B3GNTL1 CpG1 and CpG4 [adjusted for age, body mass index, and smoking: ß=-0.66, standard error (SE)=0.28; ß=-0.48, SE=0.24, respectively]. In addition, exposure to respirable dust and cumulative exposure was associated with a decrease in methylation of F2RL3 CpG2 among all welders (adjusted ß=-0.67, SE=0.23 and ß=-0.03, SE=0.02, respectively). No significant associations were found for AHRR, mitochondrial DNA copy number, or telomere length.

Conclusion Low-to-moderate exposure to welding fumes was associated with a small effect on selected early epigenetic biomarkers of cancer. The direction of the methylation pattern (lower methylation of specific CpG sites) indicates early lung cancer-related changes associated with mild steel welding.

Key terms AHRR; B3GNTL1; DNA Methylation; F2RL3; lung cancer; mitochondrial DNA; occupational exposure; respirable dust; telomere length.

Welders are exposed to high levels of welding particles (fine and ultrafine), gases, and ultraviolet radiation, and in some cases, co-exposure to asbestos and solvents may take place (1). In 2017, the International Agency for Research on Cancer (IARC) classified welding fumes as "carcinogenic to humans" (Group 1) (1, 2). This classification was based on epidemiological studies showing an increased lung cancer risk in welders and is valid for both mild and stainless steel welding (2). The main carcinogenic components of welding fumes are considered to be respirable particles that are 20-1000 nm in size and consist of a mixture of different metals, such as iron, manganese, chromium, and nickel. However, the composition of welding fumes varies, depending on the type of electrode used (mild steel or stainless steel) as well as the type of welding process (eg, gas or arc welding) and coating of the metals.

Protection of workers from adverse effects of welding fumes, including setting relevant occupational exposure limits (OEL), remains an important concern for public health. Worldwide, approximately 11 million people work as welders and an additional 110 million are exposed to welding particles at work (1). In Sweden, 13 000 people work as welders (3) and >250 000 are exposed to welding fumes at work (4). The Swedish occupational exposure limit (OEL) is 2.5 mg/m3 for inorganic respirable dust (5), however, this OEL is not health-based. Thus, it is also not clear if this limit is sufficiently protective with regard to cancer risk. In a cohort study from 2008, an increased risk for lung cancer was observed among 'ever welders' [standardized incident ratio: 1.35, 95% confidence interval (CI) 1.06-1.70], with suggested dose-response associations with duration of welding as well as cumulative exposure (6). Moreover, a cohort study and two casecontrol studies found associations between occupational welding and lung cancer (7-9).

The mechanisms underlying the carcinogenicity of welding fumes are not fully understood and numerous mechanisms have been suggested. Studies have reported systematic inflammation (10, 11), oxidative stress (12,

13), and immune suppression (14) among welders following exposure to welding fumes. Previously, our cross-sectional studies of low-to-moderately exposed Swedish welders found only limited evidence of inflammation and mild increased oxidative stress measured as 8-hydroxydeoxyguanosine in urine (15, 16). We did, however, find changes in cancer-related biomarkers: shorter telomeres (16), an increase in mitochondrial DNA copy number (mtDNAcn) among welders compared to controls (17). A more recent study observed associations with cancer-related proteins (18).

Telomeres, the repetitive DNA sequence (TTAGGG) at the end of the chromosomes, help maintain DNA integrity (19). During mitosis, telomeres shorten, and the telomere length (TL) limits how many times a cell can divide. Lifestyle factors and occupational and environmental stressors can accelerate telomere shortening or induce increases in TL. Shorter telomeres can result in chromosomal aberrations (20), a key change in carcinogenesis, whereas longer telomeres may result in higher proliferative potential and accumulation of mutations (21). Earlier case-control studies of lung cancer have shown shorter telomeres among lung cancer cases (22, 23), but more recent case-control and prospective studies revealed longer telomeres in association with lung cancer, especially adenocarcinomas (24-28).

The mtDNAcn provides another biomarker for early cancer-associated changes. The mitochondrial DNA (mtDNA) lacks introns and histones, and has a limited capacity for DNA repair, making it vulnerable to oxidative DNA damage (29). A prospective cohort study of male smokers from Southwest Finland suggested that mtDNAcn increases in cancer patients compensating for the low mtDNA functionality (30).

Changes in DNA methylation of CpG sites of cancerrelated genes play a major role in cancer and are specific for some carcinogens (31). Tobacco smoking has repeatedly been associated with hypomethylation of specific CpG sites in genes such as AHRR (encoding aryl-hydrocarbon receptor repressor) and F2RL3 (encoding F2R like thrombin/trypsin receptor 3) (32) in peripheral blood cells. Hypomethylation of cg03636183 in F2RL3 (referred to as F2RL3 CpG2 in the current study) predicts lung cancer risk (33-35). Our previous cross-sectional study of non-smoking welders showed that F2RL3 CpG2 hypomethylation was associated with working as a welder, previous smoking, and exposure to respirable dust (36). Additional evidence shows that lower CpG cg05575921 methylation in AHRR (referred to as: AHRR CpG3 in the current study) predicts lung cancer and lymphoblastic leukemia (34). Hypomethylation of PC (pyruvate carboxylase; CpG cg10151248) and B3GNTL1 (beta1,3-N-acetylglucosaminyltransferase-like protein 1; CpG cg13482620; referred to as B3GNTL1 CpG6 in the current study), were also shown to be associated with lung cancer development independent of smoking in a recent cohort study (37). Therefore, exploration of epigenetic changes provides useful information to assess cancer risk.

The aim of this study was to evaluate early cancerrelated changes, including TL, mtDNAcn, and DNA methylation of selected genes, in a cohort of Swedish welders exposed to low-to-moderate levels of welding fumes and measured six years apart.

Methods

Study design

A cohort of male welders and non-exposed controls from southern Sweden (Södra sjukvårdregionen) was established in 2010 (15). Baseline examination (timepoint 1) included 101 welders working in small- and mediumsized welding companies, and 127 age-matched controls working as gardeners and janitors for a municipality or as workers in food-storage facilities. The control group had very low or no occupational exposure to particles, including welding fumes (15). Inclusion criteria were being a non-smoker for at least the previous six months and being male. Follow-up was conducted six years after the baseline recruitment (years 2016/2017, timepoint 2). The drop-out rate was 23% (N=23) among welders and 24% (N=31) among controls; mainly due to retirement and closing of one of the companies. During follow-up additionally 70 welders and 40 controls were recruited. Based on the questionnaire data a few current smokers, who had been nonsmokers at baseline, were identified at timepoint 2 (2 welders, 3 controls).

In total, the study cohort included 338 individuals: 171 welders and 167 controls. Of these 338 individuals, 142 (78 welders, 96 controls) were examined at both timepoint 1 and timepoint 2, whereas 164 were examined only at

timepoint 1 or timepoint 2 (93 welders, 71 controls).
All participants were asked to complete a questionnaire, including questions about country of birth, education, personal and family history of cancer, diet, physical activity, smoking history, use of snus (Swedish moist tobacco), alcohol, current residency, as well as exposure to particle/ smoke during leisure time.
Peripheral blood from welders and controls was collected at both timepoints by the same nurse.
Exposure assessment
A structured questionnaire was used for controls and welders to gain information about their occupational history, including their present and past workplaces, type and duration of jobs, and whether they were exposed to welding or diesel fumes. Additionally, welders were asked about the type of welding they performed at work, how many hours they spent welding on average per work week, their individual work station, use of area-level or point-source exhaust, as well as their use of personal respiratory, noise, and eye protection devices while welding.
Personal respirable dust measurements
Personal sampling of respirable dust was performed for the welders and area-level dust monitoring was performed for the controls. A detailed description can be found in previous publications (16, 18, 38). Based on measurements from timepoint 2, the major elements in the welding fumes were iron and manganese (iron median exposure 0.5515 mg/m3; manganese 0.0896 mg/m3), whereas exposure to chromium and nickel was at much lower levels (chromium median exposure 0.0004 mg/m3; nickel 0.0005 mg/m3) as described in an earlier paper (39).
The measured respirable dust concentrations were corrected for use of protective devices by a correction factor of 3, as described in earlier papers (16, 18, 38). At timepoint 2, five welders had new or different personal protective devices compared to at timepoint 1. One welder upgraded to a half-mask (correction factor of 2), whereas four welders had a new version of a powered air purifying respirator with a double visor (correction factor of 50).
To determine the respirable dust, the filtered samples were gravimetrically analyzed according to a validated method (40). The limit of detection was 0.05 mg/sample.
For welders with missing exposure data, we based their exposure on data from welders working in the same company and with the same work tasks.
At timepoint 1, 53 out of 101 welders had measured respirable dust concentrations and 48 had estimated concentrations. At timepoint 2, 103 welders had measured respirable dust concentrations, 20 had estimated concentrations, and no data was available for 22 welders. Finally, 22 welders had measured respirable dust concentrations for both timepoints 1 and 2.
Detailed information about area level dust monitoring in the control companies have been published previously (15, 18).
To reflect the actual exposure, respiratory dust concentrations adjusted for personal respiratory protection were used in the calculation of the cumulative exposure and the statistical analysis.
Cumulative exposure
The cumulative exposure (or cumulative dose) for timepoint 1 was estimated by multiplying the respirable dust data (adjusted by use of personal protection devices) and the reported years spent welding (18). Similar calculations were made for timepoint 2, adding the estimate from timepoint 1.
Telomere length, mtDNA copy number, and DNA methylation
DNA extraction from peripheral blood samples of welders and controls was done using the QIAmp DNA Blood Midi kit (Qiagen, Hilden, Germany). Relative TL was measured using quantitative PCR (qPCR) (LightCycler 480, Roche, Basel, Switzerland) applying a SYBR Green-based assay established by Cawthon (41) as previously described (42, 43) with minor adjustments.
Similarly, the relative mtDNAcn was measured as the M/S ratio, with M as the mtDNAcn and S as the single-copy gene HBB.
Eleven CpG sites were investigated: three in AHRR (CpG1-CpG3 [CpG3 corresponds to cg05575921 Illumina 450K]), two in F2RL3 (CpG1 and CpG2 [corresponds to cg03636183]), and six in B3GNTL1 (CpG1CpG6 [CpG6 corresponds to cg13482620]). Supplementary Table 1 provides detailed information about the genomic locations of

all CpG sites.
More detailed information can be found in the supplementary material (https://www.sjweh.fi/article/3988) under methods.

Statistical analysis

The continuous variables are presented as median and 5-95th percentiles whereas categorical variables are presented as frequencies and percentages based on the total valid answers from the questionnaires. Evaluation of differences between exposure groups (welders and controls) were done with the Kruskal-Wallis rank-sum test followed by Dunn's post hoc test when comparing three groups or more; Wilcoxon Unpaired Two-Sample test was used for continuous variables when comparing two groups, and Fisher's exact test was used for categorical variables.
A detailed method description regarding differences in epigenetic biomarkers between never and ever smokers, differences between recruitment groups and the relationship between smoking and the outcome and exposure variables can be found in the supplementary material.
The correlation between selected variables of interest was analyzed using the R package corrplot. Spearman correlation was used, and the data were ordered by hierarchical clustering. The correlation coefficient was determined by the base R function contest.
Longitudinal analysis employing linear mixed models was used to evaluate associations between exposure groups and DNA biomarkers (CpG sites, mtDNAcn, TL), and fitted by using the lmer function from the lme4 package in R. Participants were included as random factors (random intercepts) in the mixed model, whereas age, body mass index (BMI), smoking (if the participants ever smoked in their life) and group were included as fixed factors. The RsgGLM function from the R package MuMin was used to calculate the explained variance by fixed factors (R2m) and random factors (R2c). P-values were adjusted for multiple testing using the BenjaminiHochberg method. Sensitivity analysis was performed including (i) only controls who never welded and (ii) only never-smokers.
Mixed models were used for evaluating associations between measurements of exposure (separate analyses for welding years, respirable dust in mg/m3 and cumulative exposure in years) and DNA biomarkers, where welders were included as random factors (random intercepts), and age, BMI, smoking (ever smoked) were included as fixed factors. Sensitivity analysis included (i) only welders with measured respirable dust data for at least one timepoint and (ii) only never-smokers.
All statistical analysis was performed in R 3.6.1 (44).

Ethical approval

The study was done in accordance with the 1964 Helsinki Declaration. All study participants gave their informed consent to take part in the study, and the Regional Ethical Committee of Lund University, Sweden, approved the study (2010/132).

Results

Characteristics of the study participants

Table 1 details the demographics and lifestyle factors of the study participants. No significant differences between welders and controls were observed in age, BMI, or smoking status, and both groups had relatively healthy lifestyles, with low alcohol consumption, regular exercise, a balanced diet, and little tobacco consumption, apart from a few 'party smokers' (table 1). No difference was observed for respirable dust levels between timepoint 1 and 2. Increases in physical activity and cancer history were found at timepoint 2 in the welding group. The respirable dust concentrations adjusted for use of personal protective equipment (PPE) showed a median of 0.7 mg/m3 at both timepoints, but there was a wider range at timepoint 1 compared to timepoint 2.
Table 2 provides information about the DNA methylation, TL, and mtDNAcn at the different timepoints. Significant differences in methylation status between never- and ever-smokers were found for five sites, all of which had higher methylation in never-smokers: AHRR CpG1 (4.6%), AHRR CpG2 (4.8%), AHRR CpG3 (5.6%), F2RL3 CpG1 (2.0%), and F2RL3 CpG2 (2.1%), as well as for mtDNAcn (0.5%) (supplementary table S2).
No significant difference in characteristics was found when comparing dropouts at timepoint 1 with the new recruits

at timepoint 2, or between dropouts at timepoint 1 and the remaining individuals. Use of snus differed between new recruits and cohort welders in timepoint 2, otherwise no differences were found (supplementary table S3).
To evaluate their relationships at each timepoint, we plotted lifestyle factors, exposure measures, and DNA biomarkers in a correlation heatmap (supplementary figure S1a and b). Age and BMI were significantly correlated with TL (age: P<0.001, rS=-0.32 at timepoint 1 and -0.31 at timepoint 2; BMI: rS=-0.19 at timepoint 1 and -0.17 at timepoint 2). The mtDNAcn was significantly positively correlated with TL (P<0.001, rS=0.25 at timepoint 1 and 0.32 at timepoint 2). Smoking status (ever- or never-smoker) was significantly correlated with differences in methylation of AHRR CpG1-3, and F2RL3 CpG1-2 (P<0.001) (supplementary table S2). Based on these significant correlations, age, BMI and smoking status were selected as covariates for the linear mixed model analysis.

Telomere length and mtDNAcn and welding

No significant differences in TL or mtDNA were observed between welders and controls or when examining different exposure measures among the welders over time (table 3, table 4).

DNA methylation and welding

Welders showed significantly lower methylation of B3GNTL1 CpG1 (P=0.016, linear mixed model analysis, adjusted for age, BMI, and ever smoking) and CpG4 (P=0.046) (table 3) compared with controls. No significant differences between exposure groups were found for AHRR or F2RL3, but effect estimates for AHRR were in general negative: all CpG sites showed lower methylation in welders compared with controls. Welders also showed an increase of methylation of B3GNTL1 CpG5 (P=0.006) compared with controls. The associations were still significant for B3GNTL1 CpG1 and CpG5 after adjusting for multiple testing.
Sensitivity analysis including (i) only controls who had never welded, showed a decrease of the effect estimates of B3GNTL1 CpG1, which became nonsignificant (P=0.076, ß=-0.54, SE=0.30) whereas the effect increased for CpG4 and remained significant (P=0.11, ß=-0.66, SE=0.26). Sensitivity analysis including (ii) only individuals who had never smoked, showed similar directions of effect estimates as the main analysis (supplementary table S4). The effect estimates increased from the main analysis for B3GNTL1 CpG1 and CpG4 and remained significant (CpG1 ß=-1, SE=0.41 and CpG4 ß=-0.69, SE=0.33). Welders also showed a significant increase in methylation of B3GNTL1 CpG5 in both sensitivity analyses: (i) P=0.012, ß=0.42, SE=0.17, (ii) P=0.014, ß=0.56, SE=0.23 (supplementary table S3).

Dose-response relationships with DNA methylation among welders

Respirable dust (adjusted for PPE) and cumulative exposure showed the strongest associations with DNA methylation in the welders (N=220-223) (table 4). A significant decrease in methylation was observed for F2RL3 CpG1 (P=0.015) and CpG2 (P=0.004) with increasing respirable dust. Cumulative exposure was also associated with lower methylation of F2RL3 CpG1 (P=<0.001) and CpG2 (P=0.048). No associations were found with welding years (N=243-245). Significance remained after adjustment for multiple testing for F2RL3 CpG1 in associations with respirable dust and cumulative exposure, and for F2RL3 CpG2 in association with respirable dust exposure.
Sensitivity analysis, including only welders with at least one measured data point for respirable dust (ie, without the welders with assessed exposure to respirable dust, N=183-186 depending on CpG site) or cumulative exposure, did not change the significance level or markedly change the effect estimates, and the results still showed a decrease in methylation with increasing exposure to welding fumes (supplementary table S5). In the sensitivity analysis of respirable dust among welders who had never smoked (N=123-125) (supplementary table S6), the association for F2RL3 CpG1 became non-significant and the effect estimates changed (from ß=-0.40, SE=0.16 to ß=0.01, SE=0.2), whereas the effect estimates for F2RL3 CpG2 remained similar, but became non-significant, to the main analysis (from ß=-0.67 SE=0.23, P=0.004 to ß=-0.59, SE=0.35, P=0.091). There was no association with cumulative exposure in welders who had never smoked (supplementary table S6).
B3GNTL1 CpG1 showed significant positive associations with respirable dust (ß=0.28, P=0.016) and cumulative exposure (ß=0.02, P=0.011) (table 4). After adjustment for multiple testing, the association with cumulative exposure remained significant.

Discussion

In this study, we investigated early lung cancer-related biomarkers in relation to occupational exposure to welding fumes. We found a significant decrease in DNA methylation of B3GNTL1 CpG1 and CpG4 in welders compared with controls. A dose-response effect was observed in that F2RL3 CpG1 and CpG2 methylation decreased with increasing personal respirable dust concentrations and cumulative exposure to welding fumes. In general, the effect estimate of the association with the selected biomarkers was subtle. However, since the respirable dust levels were below the limit of the current Swedish OEL (2.5 mg/m3), this study stresses that even exposure levels below the current OEL may be associated with epigenetic changes that could increase the risk of developing lung cancer.
B3GNTL1 encodes a transmembrane protein, has 13 exons, and is on chromosome 17; it is expressed in several tissues, including in lung tissue. The B3GNTL1 protein is involved in the metabolism of proteins and O-linked glycosylation (45), but the mechanism linking B3GNTL1 with cancer is unknown. Hypomethylation of B3GNTL1 was observed in colorectal tumors in comparison to adjacent tissue (46). More recently, hypomethylation of B3GNTL1_cg13482620 (CpG6) was associated with an increased risk of lung cancer among non-smokers (37). Here, we observed hypomethylation of B3GNTL1 CpG1 and CpG4 in welders compared with controls. These sites are close to one another, but most likely not within the regulatory region of B3GNTL1. The effect estimates of the two CpG sites increased when only including never-smokers, supporting the idea that a decrease in DNA methylation of B3GNTL1 is not associated with smoking. We did not observe a dose-response relationship in the welding group in association with welding fume exposure, actually a positive effect estimate (hypermethylation) was observed with increasing exposure to respirable dust and cumulative exposure. The demethylation of specific sites of B3GNTL1 may thus be linked to exposures we have not accounted for in our study cohort, which warrants further investigation.
In an earlier cross-sectional study at timepoint 1, we found hypomethylation of F2RL3 CpG2 in the welders, in relation to exposure to respirable dust and among earlier smokers (36). In this study, we included a second timepoint and found that exposure to respirable dust was still associated with hypomethylation of F2RL3 CpG2, and CpG1, in welders over time. Hypomethylation of F2RL3 CpG1 and CpG2 was detected in our sensitivity analysis including only welders with measured respirable dust levels as well, which suggests that exposure to welding particles may play a role in the hypomethylation of this gene. It should be noted that we did not analyze CpG3, CpG4 and CpG5 in this study.
F2RL3 is a protein-coding gene located on chromosome 19 and has two exons. It codes for protease-activated receptor-4, which is involved in the pathophysiology of neoplastic and cardiovascular disease (47). This protein takes part in blood coagulation, inflammation, and pain responses (48). Hypomethylation of F2RL3_cg03636183 (CpG2) was strongly correlated with tobacco smoking (33) as well as an increased risk of lung cancer (35). We also observed hypomethylation of F2RL3 CpG1 and CpG2 in relation to smoking in our study. However, when excluding ever-smokers from our dose-response analysis in welders, we observed a decrease in the effect estimates and the R2m values, especially for CpG1 in association with respirable dust and cumulative exposure. When we excluded all welders who had ever smoked, the number of observations decreased from 220-223 to 125, which reduced the power of the analysis and thus could explain the drop in significance and effect estimates. The similar decrease in methylation in relation to smoking and respirable dust might suggest that similar mechanisms affect the methylation pattern of specific genes; however, it is more likely that residual confounding factors interfered with our main analysis, such as tobacco consumption earlier in life.
Two of the selected methylation sites, AHRR CpG3 and F2RL3 CpG2, have been associated with tobacco smoking in previous studies (35, 49). In a recent casecontrol study (Ar=552 pairs) lower methylation of both AHRR CpG3 and F2RL3 CpG2 in blood was associated with higher risk of lung cancer and the authors proposed that DNA methylation of the two studied CpG sites might be a predictor of future lung cancer (50). When comparing the selected biomarkers between never- and ever-smokers we also observed higher methylation of more than 4% for AHRR CpG1-3 and around 2% for F2RL3 CpG1-2 in the never-smokers (supplementary table S3). Similar results were found when only including welders (supplementary table S7). No significant changes in the methylation of AHRR and F2RL3 could be observed when comparing welders and controls; however, we observed a decrease in

methylation of F2RL3 in association with welding fume exposure, but to a lower extent than of smoking. The observed differences in methylation pattern, but not between exposure groups, could be due to the changes being related to smoking. Since our cohort consists of healthy workers and the welders are exposed to low amounts of particles, it is also possible that the follow-up time was not long enough to observe changes between exposure groups.

In previous cross-sectional studies based on study participants at timepoint 1, we found shorter TL in the welders (16) as well as an increase in mtDNAcn (17). These findings could not be confirmed in this study 6 years later (timepoint 2). One possible explanation is that even though we were able to detect differences between welders and controls at timepoint 1, these differences are no longer significant when including time in our statistical model. Differences at timepoint 1 might also be due to use of different materials or PPE, without influencing the respirable dust exposure. Another possible explanation might be differences in characteristics of the dropouts and new recruits; however, no significant differences between these two groups could be observed regarding mtDNAcn or TL (supplementary table S3).

A strength of this study is that the study groups consisted of non-smoking individuals at baseline. This is important because tobacco smoking is a major risk factor for lung cancer; therefore, we were able to study epigenetic changes in a population largely unaffected by an important co-exposure factor. Our study investigated lung cancer-related markers, but we measured the effect of welding on these biomarkers in blood and not lung tissue. Nevertheless, earlier studies have shown that blood-based biomarkers like the ones in the current study can predict lung cancer risk. Still the effect sizes were rather small and need to be interpreted with some caution. Another strength is that the exposure to welding fumes was assessed using multiple different measures. Still, there may be some misclassification of exposure since we were only able to measure respirable dust on one occasion during each timepoint, the calculation of the adjusted personal respirable dust exposure may introduce errors.

In conclusion, our study showed that welders had lower methylation of B3GNTL1 CpG1 and CpG4 compared to controls as well as lower methylation of F2RL3 CpG2 in association with respirable dust and cumulative exposure. Previous studies have associated both genes with future development of lung cancer. Components within the welding fumes likely play a role in the observed epigenetic modifications. The findings stress the need to further investigate the health effects of occupational welding exposure and, if needed, to adjust the current OEL accordingly.

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Sidebar

We present new evidence of epigenetic modifications in Swedish mild steel welders. A decrease in DNA methylation, previously linked to increased lung cancer risk, was observed at exposure levels well below the Swedish occupational exposure limit (2.5 mg/m3). Therefore, we show that the current occupational exposure limit is not sufficient at protecting against early cancer-related changes.

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Additional material

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

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DETAILS

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Exposure to a SARS-CoV-2 infection at work: development of an international job exposure matrix (COVID-19-JEM)

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ABSTRACT (ENGLISH)

Objective This study aimed to construct a job exposure matrix (JEM) for risk of becoming infected with the SARS-CoV-2 virus in an occupational setting. Methods Experts in occupational epidemiology from three European countries (Denmark, The Netherlands and the United Kingdom) defined the relevant exposure and workplace characteristics with regard to possible exposure to the SARS-CoV-2 virus. In an iterative process, experts rated the different dimensions of the COVID-19-JEM for each job title within the International Standard Classification of Occupations system 2008 (ISCO-08). Agreement scores, weighted kappas, and variances were estimated. Results The COVID-19-JEM contains four determinants of transmission risk [number of people, nature of contacts, contaminated workspaces and location (indoors or outdoors)], two mitigation measures (social distancing and face covering), and two factors for precarious work (income insecurity and proportion of migrants). Agreement scores ranged from 0.27 [95% confidence interval (CI) 0.25-0.29] for 'migrants' to 0.76 (95% CI 0.74-0.78) for 'nature of contacts'. Weighted kappas indicated moderate-to-good agreement for all dimensions [ranging from 0.60 (95% CI 0.60-0.60) for 'face covering' to 0.80 (95% CI 0.80-0.80) for 'contaminated workspaces'], except for 'migrants' (0.14 (95% CI -0.07-0.36). As country differences remained after several consensus exercises, the COVID-19-JEM also has a country-axis. Conclusions The COVID-19-JEM assesses the risk at population level using eight dimensions related to SARS-COV-2 infections at work and will improve our ability to investigate work-related risk factors in epidemiological studies. The dimensions of the COVID-19-JEM could also be valuable for other future communicable diseases in the workplace.

FULL TEXT

Headnote

Objective This study aimed to construct a job exposure matrix (JEM) for risk of becoming infected with the SARS-CoV-2 virus in an occupational setting. Methods Experts in occupational epidemiology from three European countries (Denmark, The Netherlands and the United Kingdom) defined the relevant exposure and workplace characteristics with regard to possible exposure to the SARS-CoV-2 virus. In an iterative process, experts rated the different dimensions of the COVID-19-JEM for each job title within the International Standard Classification of Occupations system 2008 (ISCO-08). Agreement scores, weighted kappas, and variances were estimated. Results The COVID-19-JEM contains four determinants of transmission risk [number of people, nature of contacts, contaminated workspaces and location (indoors or outdoors)], two mitigation measures (social distancing and face covering), and two factors for precarious work (income insecurity and proportion of migrants). Agreement scores ranged from 0.27 [95% confidence interval (CI) 0.25-0.29] for 'migrants' to 0.76 (95% CI 0.74-0.78) for 'nature of contacts'. Weighted kappas indicated moderate-to-good agreement for all dimensions [ranging from 0.60 (95% CI 0.60-0.60) for 'face covering' to 0.80 (95% CI 0.80-0.80) for 'contaminated workspaces'], except for 'migrants' (0.14 (95% CI -0.07-0.36). As country differences remained after several consensus exercises, the COVID-19-JEM also has a country-axis. Conclusions The COVID-19-JEM assesses the risk at population level using eight dimensions related to SARS-COV-2 infections at work and will improve our ability to investigate work-related risk factors in epidemiological studies. The dimensions of the COVID-19-JEM could also be valuable for other future communicable diseases in the workplace.

Key terms COVID-19; mitigation factor; precarious work; transmission risk; variance.

After a new type of coronavirus (SARS-CoV-2) surfaced at the end of 2019, the incidence of coronavi - rus-disease-2019 (COVID-19) rapidly increased with a substantial number of fatalities across all countries in the world (1). Governments implemented measures to change population behaviors and limit social contacts outside the household to curb the infection curve. The so-called 'lockdowns' have far-reaching consequences, also for the working population. Worldwide, workers were encouraged to work from home whenever possible, while essential workers - who are vital for the core function of the society - remained at work, and therefore potentially in contact with co-workers, members of the general public or patients, and thus potentially exposed to the virus. Closure of specific sectors (eg, education, entertainment industry, and accommodation and food service activities) for certain periods was also implemented, and the closure patterns differed between and within countries over time (2). In between the periods of lockdowns, some occupations such as teachers, hairdressers, waiters and retailers went back to work, while other occupations were encouraged to continue to work from home.

For workers in occupations where it is not able to work from home, the workplace will contribute to the overall risk of becoming infected with SARS-CoV-2 (3). A study in the United States showed that approximately 10% of all workers are employed in occupations where exposure to disease or infection occurs at least once per week (4). The risk of getting infected with SARS-CoV-2 depends on the potential of being in contact with infected people, the characteristics of the work environment (eg, inside/ outside, ventilation) and the presence of mitigating measures such as distancing and personal protective equipment. For example, a rapid increase in SARS-CoV-2 infections during the first months of the pandemic was observed amongst frontline healthcare workers (5-9). However, due to the increasing availability and prevailing use of face coverings and other preventive measures, widespread nosocomial transmission between workers and patients reduced (10, 11). Besides healthcare workers, there is a long list of jobs in which workers are at increased risk of a SARS-CoV-2 infection, usually because their activities require close proximity to the general public. For example, security guards and taxi drivers had the highest mortality rates of all workers during the first weeks of the COVID19 pandemic in England (12). Jobs reported to have high a risk of infection included hairdressers and public transport drivers in The Netherlands (13) and bartenders, transport conductors and travel stewards in Norway (11).

In addition, COVID-19 outbreaks were described in essential sectors, such as agriculture and meat processing, where many (migrant) workers face poor working conditions. This may often involve working in close proximity with

each other with no or limited protective measures, with limited test capacity and working and where workers may also share travel and domestic arrangements (14-17). Workers with such precarious jobs (18) may be at higher risk of being infected with SARS-CoV-2 due to financial barriers that may reduce ability to self-isolate.

Workplaces may be one of the key settings in the spread of SARS-COV-2 infections, among both essential and non-essential workers. It is therefore important to assess the occupations at increased risk of exposure to SARS-CoV-2 in large study populations. A job exposure matrix (JEM) is a common tool to classify job titles by degree of occupational exposure to a potential health hazard in epidemiological studies (19, 20). As obtaining exposure data on SARS-CoV-2 at the individual level is difficult in many countries, if not impossible considering the time scales involved, a specific JEM for the occupational exposure to SARS-CoV-2 can be useful as a quick and systematic means of converting occupations into estimates of exposure. Such a JEM will enhance the investigation of the role of the workplace in the spread of the SARS-CoV-2 infection and subsequent cases of COVID-19 disease. Moreover, insight into occupations at higher risk of becoming infected with an airborne virus due to the working conditions (ie, risk for transmission and mitigation measures) can also be valuable in relation to influenza or other potential airborne spread diseases (21). In addition to national attempts to estimate the risk of SARS-CoV-2 infection in specific occupations (4, 7, 11, 13) or development of national JEM (22), there is a need to construct a harmonized JEM that is applicable across various countries. Therefore, the aim of the current study was to describe the development of an international JEM for jobs with an increasing risk of cases of COVID-19, the COVID-19-JEM.

Methods

Expert group

A JEM for the risk of becoming infected with the SARSCoV-2 virus was constructed based on expert assessment and national data. Ten experts in occupational epidemiology and exposure assessment from three different European countries (ie, The Netherlands, Denmark and the United Kingdom) were involved. Three members of the expert team drafted the initial proposal for relevant exposure and workplace characteristics to be included in the COVID-19-JEM. All members of the expert group were involved in the subsequent consensus discussions towards finalizing this proposal to establish the relevant COVID-19-JEM dimensions and their interpretation, as well as the corresponding risk ratings required. The risk ratings, explained in more detail below, were independently provided by nine of the experts. Regular online meetings were organized to guarantee efficient communication and consensus agreements within and between countries.

Framework for constructing the COVID-19-JEM

The framework for developing the COVID-19-JEM was based on four principles.

Number, nature of contacts and proximity of contact. Workers face higher risks of becoming infected when work- ing in close proximity to each other (eg, construction worker, meatpacker), and/or members of the public (eg, hairdresser, teacher), and/or patients with (suspicion of) COVID-19 (eg, healthcare worker). Thus, the COVID-19-JEM should take into account the nature and frequency of daily contacts with other persons (23).

Work location. Transmission patterns may be influenced by the working environment. It is obvious that working from home will reduce transmission. Likewise, working outdoors may reduce the risk of transmission compared to working indoors, especially when ventilation is poor.

Mitigation measures. The risk for COVID-19 depends also on the prevention and mitigation measures available and implemented. Control measures of interest are social distancing and the use of face covering.

Precarious work. The work environment will be influenced by the employment relationship. In the context of the COVID-19-JEM, precarious work is of particular interest as temporary jobs, multiple jobs, and/or insecure jobs typically involve poorer working conditions (24) and an increased risk for less stringent enforcement of mitigation actions. Similarly, migrants are often employed in precarious work, and their risk of becoming infected may be amplified by poor housing and commuting conditions, such as crowding and inadequate ventilation (25).

Dimensions in the COVID-19-JEM

The above principles were translated into eight dimensions within the COVID-19-JEM: four determinants of transmission risk, two mitigation measures, and two factors on precarious work.

The first determinant of transmission risk captured the number of fellow workers in close vicinity to each other on a regular workday. The second dimension focused on the nature of contacts, which can be coworkers, the general public or patients with (suspected) COVID-19, while the third dimension addressed the frequency and nature of contact with potentially contaminated work surfaces and materials. The fourth determinant of transmission was the working environment - ie, whether working in- or outdoors for part or most of the workday.

The mitigation measures distinguished social distancing and use of face coverings. Social distancing was defined as maintaining a distancing of >1 meter between colleagues or members of the public while at work, as advised by the WHO (26). The face covering dimension assessed the likelihood that workers wear face coverings whilst working in close proximity to colleagues or members of the public. Face coverings were considered to prevent or reduce the spread of infection and could include surgical masks, face shields or similar equipment. Some workers will also have access to respiratory protective equipment (RPE), and the assessment determines the likelihood that face covering or RPE is used during interaction with co-workers, general public or patients.

Precarious work is a multifaceted concept, and we focused on income insecurity and first-generation migrants as key aspects of precarious employment (18). For each job title, the income insecurity was rated as proportion of workers with a flexible labor contract, defined as a type of contract where a national or local mitigation measure, such as lockdown of bars, restaurants, and shops, would result in a drop in disposable personal income at the short-term. This may include zero-hour contracts, casual work, and day labor. The second dimension is the proportion of migrants in each job, whereby we did not distinguish by educational level.

For each of the four determinants of transmission risk and two mitigation measures, the level of risk was rated at four levels: no, low, elevated, and high risk. Specific rules were developed to guide the expert rater in classifying the risk (table 1). Both factors of precarious workers were also categorized into four levels, based on the proportion per job title: <1, 1-10, 11-25 or >25%. With regard to precarious work, experts from the UK relied on data from national statistics to estimate the risks per job title, whereas the estimates in Denmark and The Netherlands relied on expert's assessment as objective data on precarious work could not be easily distracted in these countries.

Cut-off values for the risks per dimension and rules were developed based on consensus among all experts.

Default setting

As the COVID-19 pandemic and governmental measures differ over time and between countries, a default setting was defined relevant to the situation to which the COVID-19-JEM refers. This default setting was defined as the situation where general mitigation measures are present (social distancing, washing hands, face covering) but the country is not under full lockdown and where vaccination has not started yet. In other words, hairdresser, construction workers and teachers are working at the worksite, while most office workers are still required to work from home.

Expert assessment step-by-step

The COVID-19-JEM was developed based on the International Standard Classification of Occupations 2008 (ISCO-08) coding scheme with four-digit codes describing 436 job titles. The iterative development process consisted of four steps and a standardized protocol was developed to follow throughout the implementation of every step.

Independent expert rating (step 1)

The experts independently rated all six dimensions of the risk of transmission and mitigation measures of the COVID-19-JEM for each job title included in ISCO-08. As the risk to be infected with SARS-CoV-2 might differ among workers within sub-industries of especially the healthcare sector, the sublevel of industry according to the nomenclature of economic activities (NACE) classification (8610-8890) (27) was added to seven jobs titles (2221, 2240, 2269, 2635, 3253, 3256, 3259).

Group expert meeting and revision (step 2)

All experts discussed the difficulties in the interpretation of the dimensions for the risk of transmission and mitigation measures overall and within specific job titles. If too many uncertainties were present, the definition of the dimensions involved were reconsidered and tailored accordingly. Part of this process was the provision of concrete examples regarding job titles where uncertainties were experienced. Afterwards, all experts independently revised

their individual ratings where needed.

Independent country rating (step 3)

Once the revised individual ratings were obtained, meetings for discussing differences and reaching consensus between the experts within each country were established. Rules on consensus per job title and dimension were established a priori. For differences in risk scores of one point between any pair of raters, and if all country raters deemed the job to be exposed, the majority rating was applied. If there was disagreement whether the job should be classified as unexposed, a discussion to reach consensus followed. For differences of >2 points, the majority rule was applied as default, but the score could be adapted based on the discussions among the raters.

Consensus between countries (step 4)

Lastly, a meeting involving one expert per country was held to discuss the observed differences between countries, primarily concerning assessments of job titles perceived as non-exposed in some countries and as exposed in others. Discussions focused on whether the observed differences were reflecting actual differences between the countries or whether they were the result of different interpretations. In the latter case, the assessment was reconsidered within each country.

Additionally, three experts discussed the definitions for the two factors on precarious work after comparing preliminary results from each country. Thereafter, each country independently provided revised input for the two factors on precarious work.

Statistical analyses

For each step, the mean, standard deviation (SD) and variance components of the assigned ratings per job title were calculated. Additionally, three performance indicators were used to evaluate the reliability and agreement between raters: (i) an agreement score, (ii) the weighted kappa, and (iii) the variance. These indicators were estimated as overall score between and within each country for each dimension (ie, raters nested within countries). An agreement score can range from 0 (0%) to 1 (100%) where the latter means total agreement between experts (28). The weighted kappa coefficient also measures agreement but takes into account that agreement may occur by chance. Kappa values were classified according to Cohen, as follows: poor (<0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80) and excellent (0.81-1) agreement (29).

For step 1 (ie, independent expert rating) and step 2 (group expert meeting and revision), agreements scores and kappas were estimated overall and per country. A hierarchical analysis of variance was conducted to determine which level contributes most to the observed variance. The rankings of three raters per country were nested within job titles to provide insight into withinjob variance due to raters and between-job variance for each country. Subsequently, job titles were also nested within country to evaluate whether job rankings differed across countries. This approach allowed components of variance to be attributed to raters, jobs, and countries.

Because step 3 (independent country rating) and step 4 (consensus among countries) included one risk score for each country, agreement scores and weighted kappas were only estimated overall as the variance could only distinguish variance by job title and country. In step 4, this procedure was also conducted for the two factors of precarious work.

All estimations were conducted in R version 4.0.2.

The definitions and risk scores assignments of the COVID-19-JEM including the eight dimensions are presented in table 1. The final risk scores on the eight dimensions of the COVID-19-JEM are presented for all three countries separately (supplementary material, https://www.sjweh.fi/article/3998, tables S1.1-S1.3). Figure 1 shows the proportion of jobs in each risk category for all eight dimensions. The proportion of job titles with a high risk was the largest for 'location' and 'contaminated workspaces' across all countries. The proportion of job titles rated as non-exposed based on transmission and mitigation factors were the largest in The Netherlands, except for contaminated workspaces which was the largest in the UK. Denmark showed the smallest proportions of precarious work in the job titles. As an illustration of the ratings, table 2 shows six job titles and their risk for each dimension in each country.

Independent expert rating (step 1)

The agreement scores of the independent expert ratings ranged from 0.46 (95% CI 0.46-0.49) for 'face covering' to

0.71 (95% CI 0.69-0.74) for 'location' (table 3). The lower agreement in 'face covering' is also reflected by the variance, as 67.0% of the variance was attributed to differences between raters and 14.0% to differences between countries. The performance of the COVID-19JEM for the other five dimensions (number of people, nature of contacts, contaminated workspaces, location and social distancing) was moderate with >50% of the variance at job level. Weighted kappas varied between poor [0.17 (95% CI 0.12-0.22) for 'face covering')] to good [0.67 (95% CI 0.67-0.67 for 'social distancing')].

Patterns for agreement scores were similar in all countries (supplementary table S2.2). The highest agreement scores were found for 'nature of contacts' and 'location' in all countries and the lowest for 'face covering' in Denmark [0.40 (95% CI 0.37-0.42)] and The Netherlands [0.39 (95% CI 0.37-0.42)]. The lowest variance by job group level was for 'face covering' in Denmark (9.2%) and The Netherlands (23.9%).

Group expert meeting and revision (step 2)

During the group meeting a need for adjustment of the definitions for the 'face covering' and 'number of people' dimensions was recognized and applied. This revision resulted in generally in slightly changes on the agreement scores, weighted kappas and variance components overall (table 3).

The agreement score for 'face covering' increased to moderate [0.54 (95% CI 0.51-0.56)] and the kappa increased to fair [0.34 (95% CI 0.31-0.37)]. The variance by job title was 34%, mainly due to higher variance at job level in Denmark and The Netherlands (supplementary table S2.3).

Independent country rating (step 3)

After the consensus meeting within each country, agreements scores improved for all four dimensions of risk transmission and two mitigation measures, with the largest improvement for 'face covering' (0.70 (95% CI 0.67-0.72); table 3). Weighted kappas ranged from moderate [0.55 (95% CI 0.50-0.60 for 'location')] to good [0.75 (95% CI 0.75-0.75) for 'contaminated workspaces']. The variance by job title reached 100% for nature of contacts, contaminated workspaces and social distancing.

Consensus between countries (step 4)

Comparisons and discussions of differences in assessments between countries led to changes in scores for some job titles, whereas scores for the vast majority remained unchanged, reflecting some perceived actual differences in working conditions between countries. As an example, a debt collector was considered a home worker in Denmark, but not in The Netherlands or the UK (table 2).

This last step slightly improved the agreement scores and weighted kappas (table 3). 'Number of people' had the lowest agreement scores [0.58 (95% CI 0.55-0.61)] while 'location' had the highest agreement score [0.77 (95% CI 0.75-0.79)]. The weighted kappas ranged from moderate [0.60 (95% CI 0.60-0.60 for 'face covering')] to excellent [0.80 (95% CI 0.80-0.80 for 'contaminated workspaces')]. The variance by job group ranged from 96% for 'social distancing' tot 99.6% for 'nature of contacts'.

In this step, the scores of precarious work were also added to the COVID-19-JEM. Due to the differences between countries, the agreement score [0.27 (95% CI 0.25-0.29)] and weighted kappa [0.14 (95% CI -0.070.36)] were poor for the dimension 'migrants', but both performance indicators were moderate for 'income insecurity' [agreement score of 0.66 (95% CI 0.64-0.69) and weighted kappa of 0.53 (95% CI 0.42-0.64); table 3].

Discussion

The COVID-19-JEM contains four determinants of risk transmission (number of people, nature of contact, contaminated workspaces and location), two mitigation factors (social distancing and face covering) and two factors for precarious work (income insecurity and migrants). Based on an iterative process with four steps involving ten experts from three countries (Denmark, The Netherlands and the UK), all 436 job titles of the four-digit ISCO-08 coding scheme were assigned a risk score ranging from 0-3 for the eight dimensions. The final COVID-19-JEM generally showed moderate to good agreement between raters, except for the dimension 'migrants'. Inter-rater reliability was good to excellent for most dimensions, except for 'migrants' and 'face covering' which showed a poor and moderate reliability, respectively.

As the occupational setting plays an important role in outbreaks of COVID-19 at a local level (30), constructing an

accessible COVID-19-JEM is a first step to assess occupational risk at a population level. Within the process, improvements in agreement and inter-rated reliability appeared for each step of the development process, after in-depth discussions within and between countries. In general, the experts between countries agreed whether workers were exposed or not, but more often disagreed on the extent to which this exposure occurred. As it was acknowledged that some actual differences between countries exist, we did not attempt to develop one general COVID-19-JEM. Instead, the coun- try specific assessments for Denmark, The Netherlands and the UK are presented separately. When applying the COVID-19-JEM in future research, researchers need to be aware of the differences between the country of interest and the countries included in this COVID-19-JEM. While transmission risk and mitigation measures are rather similar across countries, larger differences may be present in precarious work. For implementation, it is therefore recommended to select the country-axis with the highest similarities of the population under study on transmission risk and mitigation measures and to carefully investigate whether risk scores should be adapted for the country under study. With regard to precarious work, the scores need to be translated towards the specific country, or even specific province or state.

The final two dimensions of the COVID-19-JEM relate to precarious work were the proportion of workers with income insecurity due to the pandemic and the proportion of migrants. The importance of these factors was emphasized in a recent Canadian study, showing that workers in low-income occupations were at the highest risk of developing COVID-19 (31). It should be noted that the proportion of workers with income insecurity and the proportion of migrants might largely differ between countries and regions due to labor market regulation, economic composition and welfare systems (32). This is also reflected in the current study by the poor agreement and low weighted kappa for migrants between countries. Additionally, the UK used national statistics to provide input on the dimensions for precarious work and experts in The Netherlands and Denmark rated these dimensions by themselves, which might also influenced the differences between countries. Because of the large differences between country - and even regions within countries - it is recommended to adjust the precarious work factors of the selected COVID-19JEM to the population under study. Furthermore, these findings suggest that the need for tailoring precarious work-related dimensions to the population/country at hand expands likely to multinational JEM for exposures other than COVID-19.

The current study described the development and presentation of the COVID-19-JEM, and the next step to take is the validation of the risk scores per job title and estimate the associations of these dimensions with the prevalence of infections per job title from large (administrative) observational data. A first small step on validation has been conducted in the UK, whereby the COVID-19-JEM risk scores were translated from the ISCO-08 to SOC2010 codes (33). These risk scores within each dimension were validated by comparing them with infection survey data from the Office of National Statistics (ONS). The preliminary results on this small dataset showed that a small increase in the proportion of COVID-19 infected persons was observed with increasing risk scores in each dimension of the COVID-19-JEM. When reliable objective data on sufficient numbers of COVID-19 infections from all three countries is available, research on the validation of the COVID-19-JEM will continue. To further encourage other researchers to apply the COVID-19-JEM, it is freely accessible through the OMEGA-NET website and presented in the supplementary material. Furthermore, researchers need to be aware that the COVID-19-JEM in the current study is developed assuming a "basic state" of the pandemic, in which general measures are taken (social distancing, washing hands, face covering in public places, working from home as possible) but without closure of sectors. As the COVID-19-JEM might need to be specified to accommodate local conditions and measures taken, table 4 describes an example on how a multiplier can be used in order to consider the severity of the pandemic.

Additionally, the COVID-19-JEM is based on ISCO-08, which has often been used to classify jobs in large population-based studies. As the COVID-19-JEM may be applied in other studies using other occupational coding schemes such as previous versions of the ISCO, crosswalks can be used to link the ISCO-08 to other coding schemes.

The major strength of this study is the collaboration between multiple experts from three European countries within an iterative process to develop a COVID-19JEM, which resulted in improvement of agreement and reliability through

the different steps. A JEM allows for a systematic translation of jobs into exposures, which makes a JEM a highly efficient and reproducible method (20). The same approach can be used in different study populations, and the assessment is fully documented so it is transparent and adaptations can be made easily when needed for a particular country, for example.

The current study, however, is not without limitations. Firstly, the expert judgement approach to construct a JEM has been criticized for lower validity as compared to direct measurement of exposure. However, as exposure data is not available on a larger scale yet, an expert judgement approach is the only option. To optimize validity, we constructed the COVID-19-JEM with an international team consisting of nine experts and by taking a structured four-step approach. Secondly, the COVID-19-JEM consists of four risk factors for transmission, two mitigations factors and two factors for precarious work. Each dimension of precarious work was defined as the proportion of workers within each job title. Even though survey or register data potentially have a higher validity, such data was only available in the United Kingdom. This data could not easily be distracted in The Netherlands and Denmark and an expert assessment was needed. Thirdly, even though some dimensions are probably more strongly related to an infection risk than others, and collinearity exists between dimensions, future validation research is needed in studies with large samples of the workforce in order to disentangle the particular contribution of the dimensions to SARS-COV-2 infection rates. Fourthly, several variants of the virus are already spreading across the world which might have a different impact on the spread of the pandemic (34). However, the assessment of the eight dimensions are generic and independent of the "potency" of SARS-COV-2. Finally, by design, a JEM assigns the same exposure to everyone with the same job title. Heterogeneity between workers, however, will be high for the dimensions that we assessed, particularly when it is largely dependent on workers' behavior.

To conclude, the COVID-19-JEM is a first step in identifying occupations where workers are at risk of being infected with SARS-CoV-2. It consists of factors for transmission risk and mitigation as well as precarious work. The current study showed moderate-to-good agreement and inter-rater reliability on the different dimensions of the COVID-19-JEM. The COVID-19JEM is a valuable tool for future epidemiological studies on SARS-COV-2 when individual data on relevant work conditions are lacking.

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Sidebar

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DETAILS

Subject:	Infections; Agreements; Social distancing; Work environment; Epidemiology; Severe acute respiratory syndrome coronavirus 2; Essential workers; Disease control; Employment; Medical personnel; Viruses; Migrants; Disease prevention; COVID-19; Viral diseases; Exposure; Risk analysis; Ventilation; Confidence intervals; Mitigation; Severe acute respiratory syndrome; Occupational exposure; Pandemics; Working conditions; Risk factors; International standardization; Occupations; Coronaviruses; Health risks; Disease transmission
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COVID-19 mortality across occupations and secondary risks for elderly individuals in the household: A population register-based study

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ABSTRACT (ENGLISH)

Objectives This is the first population-level study to examine inequalities in COVID-19 mortality according to working-age individuals occupations and the indirect occupational effects on COVID-19 mortality of older individuals who live with them. Methods We used early-release data for the entire population of Sweden of all recorded COVID-19 deaths from 12 March 2020 to 23 February 2021, which we linked to administrative registers and occupational measures. Cox proportional hazard models assessed relative risks of COVID-19 mortality for the working-aged population registered in an occupation in December 2018 and the older population who lived with them. Results Among working aged-adults, taxi/bus drivers had the highest relative risk of COVID-19 mortality: over four times that of skilled workers in IT, economics, or administration when adjusted only for basic demographic characteristics. After adjusting for socioeconomic factors (education, income and country of birth), there are no occupational groups with clearly elevated (statistically significant) COVID-19 mortality. Neither a measure of exposure within occupations nor the share that generally can work from home were related to working-aged adults risk of COVID-19 mortality. Instead of occupational factors, traditional socioeconomic risk factors best explained variation in COVID-19 mortality. Elderly individuals, however, faced higher COVID-19 mortality risk both when living with a delivery or postal worker or worker(s) in occupations that generally work from home less, even when their socioeconomic factors are taken into account. Conclusions Inequalities in COVID-19 mortality of working-aged adults were mostly based on traditional risk factors and not on occupational divisions or characteristics in Sweden. However, older individuals living with those who likely cannot work from home or work in delivery or postal services were a vulnerable group.

FULL TEXT

Headnote

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Key terms corona virus; COVID-19 risk group; elderly mortality risk; occupational exposure; population study; work from home.

Individuals who have been particularly vulnerable to succumbing to COVID-19 include the elderly, men, ethnic minorities, and people with low educational attainment or existing illnesses (1-3). Research also clearly points to occupational differences in how the virus is spread: In Italy and the US, studies have shown that frontline healthcare workers alone made up 10-20% of all infections (4, 5). In Sweden, bus drivers, taxi drivers and pizza makers have a

significantly higher risk of infection than other workers (6). The risk of infection and death from the infection are two separate situations, however, and we know little about occupational differences in COVID-19 mortality. Some evidence points to workers in frontline or essential occupations carrying a higher risk of COVID-19 mortality, for example in California (7), Massachusetts (8), and England/Wales (9) in the early-to-mid stage of the pandemic. Given that we know traditional risk factors are not distributed equally across occupations, we can improve public health responses by assessing whether individuals work situation contributes to mortality differentials or if these risk factors operate independently of occupational exposure to coronavirus. For the elderly, who are most at risk of COVID-19 mortality (10, 11), the age-composition of households appears to play an important role in diffusion (12) and fatalities (13-15), and working-age individuals seem to increase the risk of COVID-19 mortality for elderly household members compared to those who do not live with a working-age adult (15). The role of occupational exposure is therefore potentially not only important for the individual worker but also for those sharing a living space. It may be a general pattern that workers put the older people they live with at risk or rather that specific occupations drive these patterns.

Differences in exposure risks are likely to emerge based on context-specific restrictions and recommendations related to slowing the spread of COVID-19. When countries have implemented strong lockdown measures, inequality in exposure risk is likely based on whether the individual is a frontline worker or not. When some or all restrictions are lifted or never implemented, inequality in risk emerges between those who can work from home versus those who cannot, as well as those working in public spaces or near the virus and those who do not. Sweden largely diverged from the international consensus on non-pharmaceutical interventions by never formally implementing a lockdown and instead relying on widespread normative compliance with social distancing of its population from the beginning of the pandemic. Despite not mandating a lockdown, however, Google's COVID-19 Community Mobility Reports indicate that mobility trends for workplaces decreased 25% in the country as a whole and 36% in Stockholm in March and April 2020 (16), suggesting some change of behavior in response to the global pandemic. Also, unlike other contexts, the government did not recommend personal protective equipment (PPE) such as facemasks to the public until late in the pandemic (January 2021) (17), and only then in relation to taking public transportation. The pandemic has been severe in Sweden, where COVID19 related deaths far outnumber those in neighboring and similar Nordic contexts. Taken together, Sweden provides a unique context for assessing occupational inequalities in COVID-19 mortality.

This is the first population-level study to examine inequalities in COVID-19 mortality according to working age individuals' occupations, characteristics of their occupation, and the indirect effect of this occupation on COVID-19 mortality of older individuals with whom they live. Using Swedish individual population registers, we additionally assess how occupations and their characteristics relate to the risk factors previously identified for COVID-19 mortality in Sweden. Policy responses may differ depending on whether the occupation itself poses specific risks or if COVID-19 mortality is grouped within occupations due to compositional factors.

Methods

We used the Swedish administrative and population registers that include individual-level data on a wide range of socioeconomic, demographic, and residential characteristics of all individuals living in Sweden during December 2019, and who had been resident in Sweden for at least two years. This information is linked through unique identification numbers to the cause of death register updated up until 23 February 2021, which enables us to distinguish recorded COVID-19 mortality from other causes of death.

We selected two populations for our analyses: (i) all working age individuals (20-66 years at the time of the first observation, 12 March 2020), who were registered with an occupation in December 2018 (N=4 620 395); (ii) individuals aged >67 years (a common retirement age in Sweden) on 12 March 2020 and living in a household (in December 2019) with at least one person aged 20-66 who was registered with an occupation in December 2018 (N=209 229). See supplementary material (https://www.sjweh.fi/article/3992) figure S1 for a description of exclusion of cases.

This study is produced under the Swedish Statistics Act, where privacy concerns restrict the availability of register

data for research. Aggregated data can be made available by the authors, conditional on ethical vetting. The authors access the individual-level data through Statistics Sweden's micro-online access system MONA. The Swedish ethical-vetting authority has approved the analyses, Dnr 2020-02199.

Outcome variable

We use data on all deaths reported between 12 March 2020 (the date of the first confirmed death by COVID19 in Sweden) and 23 February 2021, and whether each death was associated with COVID-19. The data on deaths contain all individuals who lived in Sweden and had been a resident in Sweden for at least two years. These data were collected by the Swedish National Board of Health and Welfare, the agency responsible for the cause of death register. In the study population of working individuals and the elderly people living with them, 12 103 individuals in our analytical sample died during the study period; the Swedish National Board of Health and Welfare reported 1355 of these as COVID-19 deaths. Of these deaths, COVID-19 was identified as the underlying cause of death in 1210 cases (ICD-10 code U07.1: 1173 deaths; U07.2: 35 deaths; or B3.42: 2 deaths). Of the remaining 145 cases, ICD-10 codes U07.1, U07.2 or B3.42 were listed as contributing causes of death but not the underlying cause of death. Our data capture two full peaks and the beginning of a third in COVID-19 mortality in Sweden and therefore the great majority of deaths in our study population in Sweden.

Occupational measures:

We applied three different measures related to occupation. Using the Swedish occupational registers, we constructed occupational groups that are widely considered to be frontline and/or essential occupations (6, 18) and in particular in the case of Sweden (6): care workers, police officers and security guards, service sector personnel, delivery workers, taxi- and bus drivers, teachers, meat packers, and cleaners. We compared the COVID-19 mortality risk of these workers (or the older individuals who live with them) to skilled workers in IT, economics, or administration, which are a large group of workers who are not considered frontline, as well as to all other occupations combined. The occupational group approach allowed us to isolate specific groups who are at risk. For a full list of the SSYK 2012 (the Swedish equivalent of ISCO-08) in each occupation, see supplementary table S1.

Whereas the frontline and/or essential worker categories focus on those who were generally required to continue working during the pandemic, our second measure focused on those who may be particularly at risk while working. It is an index combining three work context indicators, all of which are relevant to the spread of COVID-19: how much the job requires contact with others, how close the physical proximity is to people, and the frequency of exposure to disease and infection. The measure is based on publicly available data through the O·NET online database (version 24.2) (www.onetonline.org) supported by the US Department of Labor/ Employment and Training Administration. O·NET data has been applied in scientific research on health outcomes (19) as well as widely discussed in reports and media in relation to COVID-19 (20-24). The occupational exposure information has been constructed for the Standard Occupational Classification System (SOC) in the US and we matched SOC codes to the International Standard Classification of Occupations (ISCO-08). We first used the crosswalk procedure provided by Hardy et al (26), and then matched ISCO-08 codes to the Swedish Standard Classification of Occupations (SSYK 2012) with the occupational code key provided by Statistics Sweden (25). The survey questions on which the measures were constructed by O·NET, as well as the specific example of how our measure was derived for taxi drivers is presented in supplementary figure S2. Answers to these questions were standardized. As we had no basis for expecting any of these three work context dimensions to be more important than the other, we generated an unweighted mean to arrive at our occupational exposure index. The index is measured on a continuous scale of 0-100, with 100 representing constant exposure to infection, contact with others and near physical proximity. The highest score (98.7) is found for dental hygienists and the lowest score (23.8) is found for debt collectors. Supplementary figure S3 shows the distribution of our study populations across the occupational exposure measure as the share of the total, with noted examples of specific occupations.

In addition to the occupational groups and the continuous measure capturing exposure, we use a measure intended to capture the possibility of working at home in a given occupation. The measure is derived from the European Labor Force Survey (EULFS) for Sweden 2018, and constructed by the percentage in a given occupation (3 digit ISCO-08

merged to 3 digit SSYK 12) who responded that they never work from home. This measure reflects the share within an occupation in usual times and is not specific to the coronavirus pandemic, which likely means that it is a lower estimate of the share that actually were able to work from home when work was restructured due to the pandemic. Nevertheless, it should measure the overall capacity of an occupation to shift away from the workplace in times of need.

For the population aged 20-66 years, we measured one's own primary occupation, whereas for the population aged >67 years, we measured the primary occupation of other individuals aged 20-66 in the household. If there were more than one individual with an occupation in an elderly individual's household, we let any frontline/essential occupation dominate.

In the baseline models, we controlled for age, sex and whether the individual was living in Stockholm (measured at the end of 2019). In fully adjusted models, we additionally controlled for potential confounders and mediators: country of birth, highest achieved educational degree, and individual net income (measured at the end of 2018).

We performed Cox proportional hazard regressions with COVID-19 death as an event, with the log of age as an offset in the models (27). The follow-up time began 12 March 2020 and ended with (i) all-cause mortality between starting time and 23 February 2021 (the last reliable COVID-19 death in our data was reported at this date), or (ii) being alive on 24 February 2021. All analyses were conducted using Stata Statistical Software: Release 16 (StataCorp LP, College Station, TX, USA).

Results

Descriptive statistics of the population and covariates are available in supplementary table S2. Full model results for the working-aged and older populations are available in supplementary tables S3 and S4, respectively. The first figures display both the relationship between COVID-19 mortality and our three occupational measures, assessed independently, and how occupational differences in mortality are mediated or confounded by our set of socioeconomic status (SES) control variables (educational attainment, income and country of birth). We interpreted results both in terms of 95% and 90% confidence intervals (CI) because of the few numbers of deaths distributed over the various occupational categories. In all tables, however, only results according to 95% CI are reported.

For working-aged people, figure 1 shows that, without adjusting for SES (light grey lines), the occupations that are typically considered to be frontline are in general at a higher risk of COVID-19 mortality than skilled workers in IT, economics or administration. The only exception was the occupation of police/guard, for whom the estimated risk of COVID-19 mortality was lower than skilled workers. Taxi/bus drivers, service sector workers and cleaners have the highest relative risks of COVID-19 mortality. Taxi/bus drivers have over four times that of the skilled workers group. Net of SES (dark grey lines), taxi/bus drivers' mortality risk remains the highest [relative risk (RR) 1.41], whereas all other occupational groups shift to having a lower risk of COVID-19 mortality. The increased mortality risk for taxi/bus drivers is no longer statistically significant (P=0.26).

Occupational exposure (lower panel of figure 1), measuring closeness to/contact with others and proximity to infectious diseases, relates positively to COVID19 mortality risk, but this estimate is not statistically significant. When adjusting for SES, the relationship shifts to below 1 (indicating a lower risk of COVID19 mortality). As a robustness check, we relaxed the assumption of linearity and estimated the relationship with a quadratic and cubic term instead. These transformations did not change the result.

The share of individuals who cannot work from home in their occupation is more positively related to COVID19 mortality than exposure in the occupation. This relationship also disappears when adjusting for SES.

For older individuals who live with working-aged adult(s), figure 2 shows a few different patterns related to occupational differences. First, living with a taxi/bus driver does not add additional risk of COVID-19 mortality. Living with a cleaner or delivery and postal worker does increase the risk of COVID-19 mortality for older people, and if we consider differences using a 10% significance level, service sector and care workers are also associated with higher older age COVID-19 mortality. When adjusting for SES, the only occupational group that posed a higher risk of COVID-19 mortality for older co-residents was delivery and postal workers (adjusted for SES: RR 2.16, P=0.015). Occupational exposure was positively related to mortality risk, but this relationship was not statistically significant.

When considering the importance of working from home, we see that elderly individuals who were living with worker(s) who likely cannot work from home have a higher risk of COVID-19 mortality. This relationship persisted when we adjust for the older person's own SES (RR 1.005, P=0.001). This RR is for an increase in being able to work from home of only one percentage point, whereas the RR is 1.73 if we consider instead 100% versus 0% of an occupation not being able to work from home.

Tables 1 and 2 show how the relationship between COVID-19 and education, income and country of birth changes with and without adjusting for occupational information. Worth noting is that adding occupational information to the baseline model does not improve the model fit for either Akaike's or Bayesian information criteria (AIC/BIC), which implies that traditional risk factors such as SES explain variation in COVID-19 mortal- ity better than occupational factors and that occupational information does not contribute much to understanding COVID-19 mortality beyond what we learn from SES. This finding was consistent across both the workingaged population and the older individuals who live with a working-aged individual. We can conclude then that much, if not all, of the relationship between COVID19 mortality and occupations or their characteristics is compositional. The only exception was a lower AIC and similar BIC in the models with older individuals when adding the share that can work from home.

The relatively larger impact from traditional risk factors as compared to occupational characteristics is also confirmed by the results presented in tables 1 and 2. These models are similar to those in figures 1 and 2 and explore whether occupational factors mediate or confound the main risk factors that have been identified with COVID-19 mortality. The change in RR over the models adjusting for occupation or occupational characteristics is minimal. This also holds for country of origin. Results clearly show that the relationship between SES factors and COVID-19 mortality is mediated or confounded very little by occupational characteristics for those who are working in Sweden.

Table 2 shows a similar pattern for the older individuals, where the relationship between SES and COVID19 mortality is largely robust to the addition of occupational information of the individuals with whom they live. However, when including the measure of the share who cannot work from home, the model fit slightly improved according to the AIC and there were slight reductions across most SES indicators. We can conclude from these estimates that when older people live with individuals who can work from home, they have a lower COVID-19 mortality risk, and this is independent of the SES of the older individual.

Discussion

Our investigation into whether inequalities in COVID19 mortality appear to be related to the work environment is motivated by the inequality in worker's conditions and demands for showing up to work even in the midst of a pandemic. Frontline and essential workers have faced grave and uncertain consequences for their lives and families with the relentless spread of COVID19. Our findings provide both good and bad news related to frontline workers. First, greater exposure to people and infectious disease on its own does not appear to put workers or the elderly they live with in greater danger of COVID-19 mortality. Nevertheless, we identified a few occupational groups in which COVID-19 mortality has been much higher than others. COVID-19 mortality appears to be largely clustered within occupations according to the composition of workers in terms of educational attainment, income and country of birth.

Beyond socioeconomic characteristics, one occupational group seems to be risky for the elderly who live with them: those who are >67 years and live with younger individuals working in delivery and postal services had an elevated risk of COVID-19 mortality. In addition, we found that working in an occupation in which the capacity to work from home is low puts older individuals in the household at a heightened risk of dying from COVID-19. Both of these heightened risks persist when adjusting for older individuals' own SES. Even if older individuals limited their engagement with others to protect themselves during the pandemic, they may have still been vulnerable due to people continuing to work at workplaces combined with the lack of facemasks on public transportation.

Although the finding that pure exposure was not related to an elevated mortality risk may be counterintuitive, it is plausible in light of a few factors. First, workers who are nearest to COVID-19 (doctors and nurses) are healthcare workers, who are the most likely to be provided PPE and appropriately trained in their use. These include respiratory protection, face visors, protective aprons and protective gloves. The role of PPE in protecting workers is clear:

frontline healthcare workers in the US and UK had significantly higher risk of COVID-19 infection when PPE were not available or being re-used (28). Sweden adheres to the EU regulation 2016/425 on PPE and the Swedish Work Environment Agency regularly checks compliance. Although Sweden was unprepared for the increased need for PPE due to the pandemic according to a report issued by the leading medical associations and trade unions in March 2020 (29), workers with the highest occupational exposure were likely to have had some form of protection. The finding that occupational factors for workers do not explain more variance in COVID-19 mortality than SES should be considered in light of our focus on mortality instead of infection rates. Patterns are likely to reflect the frailty and health behavior of individuals in the occupations, which correlate with socioeconomic status (30-35). We are not able to adjust for factors such as individuals being sorted into occupations on the basis of health (32, 36, 37) or experiencing health conditions directly due to their work environment (38). Worth noting, descriptive studies may overestimate the differences between occupations in COVID-19 mortality due to confounders and mediators such as education, income and country of birth.

The possibility of super-spreader events, such as professional meetings occurring early on in the pandemic, may influence estimation of occupational risks, in which the virus is transmitted in a single work environment or occupational group, such as in the case of meatpackers in Germany and miners in northern Sweden. Our extended period, including almost an entire year and three waves of COVID-19 infections, lowers that risk. We now know that bus and taxi drivers not only have a substantially heightened COVID-19 infection risk (39) but also an elevated mortality risk. The excess risk became statistically non-significant when adjusting for individual characteristics, particularly country of birth, which is likely due to low case numbers. Because taxi and bus drivers do not spend much time together and therefore are not at risk of spreading it to each other, our finding related to this occupational group is likely generalizable. Cars and buses may be hot zones for the virus as many visitors enter and exit over the course of a shift and COVID-19 does not quickly fall out of enclosed air (40). Efforts to train and provide PPE for such drivers is therefore important.

Sweden offers a good example of conditions with low government restrictions related to the spread of COVID19. Occupational exposure likely plays a weaker role in such a context because other pathways of transmission such as restaurants, gyms, and shops remained mostly open. The extent to which our results are generalizable to other contexts may be limited as well if, for example, PPE were more widely available in Sweden or other healthcare practices were in place that protected workers better in Sweden than elsewhere. On the other hand, Sweden is also unique because it is one of the few countries that did not adopt individual mask-wearing as a practice to limit the spread of COVID-19. Were all customers to wear appropriate masks, the risk to drivers and postal workers, for example, may have been less (41). Another contextual factor to consider is whether the high-income replacement benefits for both short and long-term sick leave in Sweden influence whether individuals with poor health are in the labor market less than in contexts providing lower social benefits such as the US. This has implications for how a healthy worker effect operates within specific occupations, which would influence the differences between occupational groups, as well as how likely sickness presenteeism is, in which people who are ill do not stay home.

A few limitations of this study are important to note and involve the precision of our measures. We are not able to match occupation or income at the exact time of death. This is a problem to the extent that there was job change or a change in labor market status between the measures (December 2018) and the part of the pandemic we cover (March 2020-February 2021). We assessed the frequency of job change and labor market exit prior to the pandemic to understand how much measurement error is likely in our models. Using 2016 and 2017 as comparison, we see that 97% of working age individuals who were registered with an occupation in 2016 were also registered with one in 2017, and that 94% of these had the same occupational classifications as the one that we use in our study based on data for December 2018. Another source of measurement error relates to the measures of exposure and the share that work from home. These were both constructed in times that precede the pandemic and therefore do not capture how occupations adapted to the threat of infection. We interpret this measurement error to mean that both exposure and the share who do not work from home are generally overestimated in our data, but it is unknown how universal the overestimation is or which occupations were unable to adapt to the pandemic.

In addition, our time period covers three waves of the pandemic; no one in Sweden was vaccinated in the first and second waves, and only a small proportion of the population had been vaccinated by the end of our observation period. The results are likely not generalizable to a potential future in which vaccinations may play a more decisive role in mortality risks. To the extent that both infections and death due to infection are clustered within groups of individuals, standard errors may not be robust. Standard tools to adjust for non-independence are, however, not available given that we lack information on how observations are clustered.

In sum, our findings suggest that there are few if no real specific risk groups according to being a frontline or essential worker in a context such as Sweden in which there was no lockdown or comparably few mandated social distancing restrictions. Frontline workers may, nevertheless, still be bearing the brunt of the pandemic in Sweden even if they are not dying more. They may still be facing a higher infection risk, more sickness, extra stress, and longer work hours if more coworkers are sick.

Our findings confirm that traditional risk factors are not distributed equally across occupations. Moreover, COVID-19 mortality risk follows traditional risk factors independently of occupational factors and occupation cannot in and of itself explain observed mortality differentials among workers. However, because of our unique setting, our results cannot speak to the racial and ethnic differences emerging in other settings (42) that may be related to occupational exposure. In the US, for example, the gap between essential and non-essential workers was great in terms of who could remain at home, and this division is correlated with ethnicity and race (43). Individuals who were not born in Sweden, nevertheless, remain at higher risk of COVID-19 mortality compared to Swedish-born individuals after considering occupational factors. This is not to suggest that occupation does not contribute to the disadvantages of ethnic and racial minorities, but that inequalities are the result of more complex systemic differences (44) than can be captured by our measures. These inequalities remain an important area of future research.

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DETAILS

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Re: Videnros C, Selander J, Wiebert P, Albin M, Plato N, Borgquist S, Manjer J, Gustavsson P. Postmenopausal breast cancer and occupational exposure to chemicals

Anonymous

FULL TEXT

Re: Videnros C, Selander J, Wiebert P, Albin M, Plato N, Borgquist S, Manjer J, Gustavsson P. Postmenopausal breast cancer and occupational exposure to chemicals. Scand J Work Environ Health. 2019;45(6):642-650. doi:10.5271/sjweh.3822

by Videnros C

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Refers to the following text of the Journal: 2019;45(6):642-650

Re: Videnros C, Selander J, Wiebert P, Albin M, Plato N, Borgquist S, Manjer J, Gustavsson P. Postmenopausal breast cancer and occupational exposure to chemicals. Scand J Work Environ Health. 2079;45(6):642-650. doi:10.5271/sjweh.3822

This erratum concerns the methods section. The error relates to the adjustment for physical activity, which was made for physical activity outside of work, not for physical activity at work, as erroneously stated on page 644.

Statistical analyses

Confounding variables were selected based on a priori knowledge from the literature including age (45-49, 50-54, 55-59, 60-64, 65-69, 70-74 years), parity (0, 1, 2, 3, >4), age at first term pregnancy (<20, 20-24, 25-29, 30-34, >35 years), months of breastfeeding per child (0, 1-5, 6-12, >13), hormone replacement therapy (HRT) (no treatment, oestrogen, progesterone, combined treatment), physical activity at work (quartiles), alcohol consumption (0, I-l4, 15-30, >30 g/day), height (<160, 160-169, >170 cm) and BMI (<18.5, 18.5-24.9, 25.0-29.9, >30 kg/m2).

Should be ... "physical activity outside of work" ...

DETAILS

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Bigert, C., Kader, M., Andersson, T., Selander, J., Bodin, T., Gustavsson, P., . . . Albin, M. (2022). Night and shift work and incidence of cerebrovascular disease – a prospective cohort study of healthcare employees in stockholm. Scandinavian Journal of Work, Environment & Health, 48(1), 31-40,31A. doi:https://doi.org/10.5271/sjweh.3986

Objective This study aimed to investigate the effects of various aspects of night and shift work regarding incident cerebrovascular disease (CeVD). Methods The cohort included 26 667 women and 3793 men (nurses and nursing assistants) who were employed for at least one year 2008-2016 in Region Stockholm, Sweden. Information about the cohort and working hours were obtained from a computerized employee-register and diagnoses were retrieved from national and regional registers. We used discrete time proportional hazard models to assess the risk of CeVD (2009-2017), in relation to work hour characteristics, adjusting for sex, age, country of birth, education and profession. Results We observed an excess risk of CeVD (N=223) among employees who, during the preceding year, worked night shifts >30 times hazard ratio (HR) 1.44, 95% confidence interval (CI) 1.04-1.99] or >3 consecutive night shifts >15 times (HR 1.69, 95% CI 1.18-2.42) or with >30 quick returns (5 years) of exposure to night shift work (HR 1.87, 95% CI 1.27-2.77), all supported by a dose-response pattern. Conclusions Our results show that the risk of CeVD among nurses and nursing assistants is associated with night shift work. The number of years with night shift work, the frequency of night shifts per year, the frequency of consecutive night shifts, and short recovery after night shifts influenced the risk. Work schedules aiming at minimizing these aspects of night shift work may reduce the risk.

Harding, B. N., PhD., Castaño-Vinyals, G., PhD, Palomar-Cros, A., Papantoniou, K., PhD., Espinosa, A., M.S., Skene, Debra J,Pharm M.Sc PhD., . . . Pozo, O. J., PhD. (2022). Changes in melatonin and sex steroid hormone production among men as a result of rotating night shift work – the HORMONIT study. Scandinavian Journal of Work, Environment & Health, 48(1), 41-51,41A. doi:https://doi.org/10.5271/sjweh.3991

Objective Data from real world settings on circadian disruption and subsequent hormone-related changes may explain the higher risk of hormone-dependent cancers among night shift workers.The present study examines the melatonin and sex steroid hormone levels among night shift workers. Methods We included 44 male, rotating shift workers from a car factory in Spain, sampled both at the end of a 3-week night shift (22:00-06:00 hrs) and a 3-week early morning shift (06:00-14:00 hrs). Participants collected all urine voids over 24-hours during each shift. Urinary concentrations of sex steroid hormones (estrogens, androgens and progestogens) and 6-sulfatoxymelatonin (aMT6s, major melatonin metabolite) were determined. Individual cosinor analysis was used to derive the acrophase (peak time) and area under the curve (total production). Linear mixed models examined intraindividual associations between night shift work and log-transformed 24-hour peak time and total production of hormones compared to early morning shift work. Results The acrophase was delayed during the night shift for aMT6s geometric mean difference (GMD) 7.53 hrs, 95% confidence interval (CI) 4.46-10.60], androgens (eg, testosterone: GMD 6.83 hrs, 95% CI 0.34-13.32) and progestogens (eg, 17-hydroxyprogesterone: GMD 4.54 hrs, 95% CI 2.92-6.16) compared to the early morning shift. We found a higher production of adrenal androgen 11-oxoandrosterone/11-oxoetiocholanolone geometric mean ratio (GMR) 1.43, 95% CI 1.12-1.81], and a lower production of adrenal progestogen 16-cysteinylprogesterone (GMR 0.79, 95% CI 0.67-0.93) during the night shift compared to the early morning shift levels. Conclusions Night shift work was associated with melatonin and sex hormone-related changes in timing and total production, providing insight into the mechanistic path for its association with hormone-dependent cancer.

Jensen, J. H., PhD., Miskowiak, K. W., D.M.S.C., Purdon, S. E., PhD., Thomsen, J. F., PhD., & Eller, N. H., D.M.Sc. (2022). Screening for cognitive impairment among patients with work-related stress complaints in denmark: Validation and evaluation of objective and self-report tools. Scandinavian Journal of Work, Environment & Health, 48(1), 71-80,71A. doi:https://doi.org/10.5271/sjweh.3990

Objective Many patients with work-related stress display cognitive impairment that may hamper recovery. We examined objective and subjective tools for screening of cognitive impairment in this patient group. Methods Patients were assessed with Danish versions of the objective Screen for Cognitive Impairment in Psychiatry (SCIP-D),

standardized neuropsychological tests that tapped into the same cognitive domains, the self-assessed Cognitive Failure Questionnaire (CFQ), and several additional scales of symptom severity and psychosocial status. Concurrent validity of the SCIP-D and CFQ was assessed by calculation of Pearson's correlation coefficients between the objective and subjective tools and the scores on more conventional standardized neuropsychological tests. Decision validity was assessed with logistic receiver-operating-characteristic analyses using a cut-score approach to the objective and the subjective test results to predict impairment detected by the standardized tests. Cognitive norms were established through the data of 79 healthy controls. SCIP-D scores were compared between patients and healthy controls with independent t-tests. Results We included 82 patients with work-related stress. The SCIP-D total scores were strongly associated with standardized neuropsychological tests (r=0.76, P0.30). The optimal SCIP-D total-score cut of <72 identified 43.2% of the patients with global objective cognitive impairment. The patients performed mildly-to. moderately lower than the healthy controls on the SCIP-D total score (Cohen's d=0.39) and the subtests for working memory (d=0.39) and processing speed (d=0.61). Conclusion The SCIP-D is a valid screening tool sensitive to objective performance-based cognitive impairment among patients with work-related stress.

Pena-Gralle, A., Talbot, D., PhD., Duchaine, C. S., M.Sc, Lavigne-Robichaud, M., Trudel, X., PhD., Aubé, K., MSc, . . . Brisson, C., PhD. (2022). Job strain and effort-reward imbalance as risk factors for type 2 diabetes mellitus: A systematic review and meta-analysis of prospective studies. Scandinavian Journal of Work, Environment & Health, 48(1), 5-20,5A. doi:https://doi.org/10.5271/sjweh.3987

Objectives This systematic review and meta-analysis aimed to synthesize the available data on prospective associations between work-related stressors and the risk of type 2 diabetes mellitus (T2DM) among adult workers, according to the demand-control-support (DCS) and the effort-reward imbalance (ERI) models. Method We searched for prospective studies in PubMed, EMBASE, Web of Science, Scopus, CINHAL and PsychInfo. After screening and extraction, quality of evidence was assessed using the ROBINS-I tool adapted for observational studies. The effect estimates extracted for each cohort were synthesized using random effect models. Results We included 18 studies (reporting data on 25 cohorts) in meta-analyses for job strain, job demands, job control, social support at work and ERI. Workers exposed to job strain had a higher risk of developing T2DM when compared to unexposed workers pooled rate ratio (RR) 1.16, 95% confidence interval (CI) 1.07-1.26]. This association was robust in several supplementary analyses. For exposed women relative to unexposed women, the RR was 1.35 (95% CI 1.12-1.64). The RR of workers exposed to ERI was 1.24 (95% CI 1.08-1.42) compared to unexposed workers. Conclusions This is the first meta-analysis to find an effect of ERI on the onset of T2DM incidence. It also confirms that job strain increases the incidence of T2DM, especially among women.

Sjögren, B., Albin, M., Broberg, K., Gustavsson, P., Tinnerberg, H., & Johanson, G. (2022). An occupational exposure limit for welding fumes is urgently needed. Scandinavian Journal of Work, Environment & Health, 48(1), 1-3,1A. doi:https://doi.org/10.5271/sjweh.4002