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Occupational chemical exposures in pregnancy and fetal growth: evidence from the Born in Bradford Study

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ABSTRACT (ENGLISH)

Objectives This prospective birth cohort study evaluated the effect of occupational exposure to endocrine disrupting chemicals (EDC) during pregnancy on inadequate fetal growth as measured by small-for-gestational age (SGA) and inadequate fetal growth measured by percentage of optimal birth weight (POBW). The study also identified the maternal characteristics associated with an increased risk of exposure to EDC. Methods We studied 4142 pregnant women who were in paid employment during pregnancy and participated in a population-based, prospective 2007-2011 birth cohort study, the Born in Bradford Study, with an estimated participation of 80%. Job titles were coded at 26-28 weeks' gestation at a 4-digit level according to 353 unit groups in the 2000 UK Standard Occupational Classification. They were then linked to expert judgment on exposure to each of ten EDC groups as assessed through a job exposure matrix (JEM). We performed generalized estimation equation modelling by a modified Poisson regression to assess the risk of POBW and SGA associated with an increased risk of chemical exposures. Results The frequency of POBW<85 significantly increased for mothers exposed to pesticides [adjusted risk ratio (RR_{adj}) 3.72, 95% confidence interval (CI) 1.40-9.91] and phthalates (RR_{adj} 3.71, 95% CI 1.62-8.51). There was a 5-fold increase risk of SGA for mothers exposed to pesticides (RR_{adj} 5.45, 95% CI 1.59-18.62). Veterinary nurses and horticultural trades were most frequently associated with exposure to pesticides while hairdressers, beauticians, and printing machine minders were associated with phthalates. Conclusion Maternal occupational exposure to estimated concentrations of pesticides and phthalates is associated with impaired fetal growth.

FULL TEXT

Headnote

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Endocrine disrupting chemicals (EDC) are exogenous human-made substances that alter hormone regulation through interference with the endocrine system (1). They include many classes of chemicals such as pesticides, phthalates, polycyclic aromatic hydrocarbons (PAH), alkyl phenolic compounds (ALP), solvents, cytotoxic drugs, and anaesthetic gases. Global concerns have been raised in recent years over the potential adverse health effects of exposure to EDC (1-3). The endocrine system regulates many essential body functions such as growth, behavior, and reproduction through the controlled release of hormones (1, 4). The most sensitive windows of exposure to EDC are during fetal development and puberty (1). With an increasing number of women active in the labor force in both developed and developing countries, many will work during their reproductive years (5, 6) and likely be exposed to a variety of chemicals during pregnancy. Associations between prenatal exposure to EDC and a num1 ber of adverse pregnancy outcomes have been reported, including miscarriage (7), birth defects (8-12), stillbirth (13), small-for-gestational age (SGA) (14), impaired fetal growth (15, 16), low birthweight (LBW) (17), and preterm birth (PTB) (18). However, there are limited prospective birth cohort studies to evaluate this association and despite these investigations, evidence of such effects in humans is inconclusive, and many EDC have not yet been evaluated in epidemiological research (5).

Babies born with inadequate fetal growth are at increased risk of life-threatening health problems, as well as long-term complications and developmental delays (19-23). Inadequate fetal growth is an important predictor of perinatal morbidity and mortality, a potential risk factor for cognitive disability later in childhood and coronary heart disease and hypertension in adult life (17-21). Despite extensive research, the causes of these adverse birth outcomes are incompletely understood but factors such as sociodemographic and socioeconomic status; lifestyle; reproductive history; medical conditions, such as diabetes and hypertension during pregnancy; as well as occupational and environmental exposures may be relevant (24-27). Their association with several workrelated risk factors is well established and has resulted in legislation, for example, considering exposure to specific chemicals, such as photoresistant solvents in the semiconductor industry or antineoplastic (cytotoxic) drugs in healthcare organizations, which have been declined over the past 20 years (11, 28). However, the scientific evidence is less consistent for many other EDC.

The primary objective of this study was to assess the effects of occupational exposures to estimated concentrations of EDC on the risk of SGA and inadequate fetal growth. The secondary objective was to identify the maternal characteristics associated with an increased risk of exposure to EDC.

Methods

The Born in Bradford Study is a population-based, prospective, longitudinal, and multi-ethnic birth cohort study that recruited 12 453 pregnant women with 13 959 pregnancies during 2007-2011. With an estimated participation rate of 80%, the study monitors participants, their partners and off-spring until adulthood. Full details of the study methodology have been previously reported elsewhere (29, 30).

Study design

Figure 1 shows the selection of the study cohort. Information about job description and working conditions was collected primarily through a mid-pregnancy questionnaire at about 26-28 weeks' gestation. The questionnaire data was linked to maternity data and employment status for 11 400 pregnancies. We selected women who gave birth to a live-born singleton, were in paid employment during pregnancy, and enrolled in the Born in Bradford Study prenatally. Of 11 400 pregnancies, we excluded those with twins (N=140), triplets (N=2), stillbirths (N=59), and

missing information on pregnancy outcome (N=348). Of the 10 851 remaining, we excluded pregnancies where the mother was: not employed during pregnancy (N=2963), Of the 10 851 remaining, we excluded pregnancies where the mother was: not employed during pregnancy (N= 2963), never employed (N=2936), a student (N=348), on sick leave (N=445), and missing information on the working situation (N=17). Therefore, 4142 (38%) of mothers in paid employment during their pregnancies were eligible for analysis.

The Bradford Research Ethics Committee provided ethics approval for the study (reference 06/Q1202/48).

Working condition and occupational coding

Information concerning job title, type of business, selfemployment, and the four main tasks performed at work were used to classify the jobs according to the UK Classification of Occupations (31). We coded the job titles at a 4-digit level according to 353 unit groups in the 2000 UK Standard Occupational Classification (31). The job titles were coded and validated through the ComputerAssisted Structure Coding Tool (Cascot) (32). The coded job titles subsequently linked to an updated UK job exposure matrix (JEM) for chemical exposure developed over the same period as this cohort study (33, 34).

Exposure assessment

In 2009, Brouwers et al (34) developed this JEM, which considers the 353 job titles, adapted from the van Tongeren JEM of 2002 (33). Three occupational hygienists estimated the job-specific risk of exposure to each of ten chemicals groups: PAH, polychlorinated organic compounds, pesticides, phthalates, organic solvents, bisphenol A, ALP, brominated flame-retardants, metals, and a miscellaneous group: as unlikely (score=0), possible (score=1) or probable (score=2). In addition, broad and non-specific job titles were considered 'unclassifiable'. For this study, we collated the last two categories (possible and probable) into one indicating the occurrence of exposure to EDC was more likely than unlikely. No distinction was made between the various routes of exposure (inhalation, ingestion, or dermal). For many chemicals, most of the population experiences some level of exposure through diet or widely used consumer products. The JEM exposure score refers to the probability that the occupational exposure exceeds this background level.

Measures of birth outcomes

Information about gestational age, gender, weight, length and head circumference at birth was obtained from medical records and hospital registries to allow the following variables to be created.

Gestational age was based on the actual and estimated date of delivery calculated by the physician or midwife from the dating scan (if available) or last menstrual period.

SGA was defined as a birth weight less than the 10th customized centile, using GROW software from 2013 (35, 36), www.gestation.net/cc/about.htm (37). The calculation of SGA was derived from maternal characteristics, birth weight and gestational age data recorded in the electronic maternity system at the Bradford Research Institute.

Optimal birthweight was estimated for each birth using a model derived from a population of singletons not exposed to any of the common risk factors for growth anomaly, with terms for infant gender, gestational duration, and maternal height and parity by a method validated and corrected for births before 30 weeks' gestation (38, 39). Appropriateness of intrauterine growth is inferred from the ratio of the observed-to-optimal birth weight expressed as a percentage, percentage of optimal birth weight (POBW). The 10th percentile of weight in the original population was a POBW of 87% (38), therefore our criterion for inadequate fetal growth of POBW of <85 represents a slightly more stringent criterion than the 10th percentile, the criterion used for SGA. The method has been used in previously published studies (23, 40, 41).

Maternal characteristics / confounder assessment

The following potentially confounding factors were also solicited with the mid-term questionnaire: mother's sociodemographic, lifestyle, ethnicity, medical, and socioeconomic status [index of multiple deprivation 2010 (IMD)] as described in table 1. These characteristics are considered potential confounders for both aims of study investigation. We also considered each group of EDC as independent variables in the analysis to address the first aim of this study. Chemical exposures with numbers fewer than five records, which include polychlorinated organic compounds, bisphenol A, and flame-retardants, were not included in the analysis. As such, seven groups of

chemicals were included in the analysis.

Strategy of statistical analysis

We used univariate and multivariate analyses with risk ratios (RR) and 95% CI (CI) generated using generalized estimation equation (GEE) modelling by a modified Poisson regression, with robust error variance (42, 43). Findings at P<0.05 were considered significant. The two crude and adjusted models estimated the risk of dependent variables with independent variables as shown in tables 2 and 3. All independent variables were categorical. For example, in table 2, all co-variables were screened by cross-tabulations, Chi2 test and also the Mantel-Haenzel adjusted odds ratio (OR) with separate SGA and POBW variables. If significant at P<0.2, the co-variables were entered into fully adjusted multivariate models for both SGA and POBW. Backwardsstepwise regression was used to simplify the models by sequentially removing non-significant variables that did not reduce how well the data fitted the models. Covariates were included in the multivariate model if the difference between the crude and adjusted RR was >10% for either outcome measure. For reasons of comparison and based on evidence from previous literature, maternal age, education, alcohol consumption, and job hours were included by default, independent of statistical significance. Interaction effects were examined for statistical significance. The analysis of POBW<85 was also stratified by ethnicity. All preceding calculations were made using the statistical program STATA (StataCorp, College Station, TX, USA).

Results

Table 1 describes the maternal characteristics of the 4142 eligible pregnancies and gives crude risks of SGA (10.9%), and POBW<85 (17.9%). The cohort was multiethnic: ~60% were classified as Caucasian British, ~29% South Asian (Pakistani/Bangladesh/India), and ~11% other. The results from crude risks indicate that women were more likely to have babies with inadequate fetal growth as measured by both SGA and POBW<85, if they are from a South Asian ethnicity group, less educated, smoke, use drugs, live in most derived areas, or have preeclampsia or pre-existing hypertension.

Table 2 presents the univariate and multivariate estimates of RR for each of the two outcomes associated with statistically significant risk factors. In the multivariate analyses, all maternal characteristics and each category of seven groups of chemicals (those with numbers more than five records) were included except vitamin/iron supplementation and financial status, which were not statistically significant. There were no significant differences between occupational groups for either outcome. However, work involving standing most of time was associated with a 25% increased risk of having a baby with inadequate fetal growth.

Effects of EDC on the risk of SGA

In multivariate analysis, the proportion of infants with SGA among women likely occupationally exposed to PAH, pesticides, phthalates, or ALP was statistically non-significantly higher than among women in the refer- ence group, except for exposure to pesticides where it was 5 fold higher [adjusted RR (RRadj) 5.45, 95% CI 1.59-18.62]. No association was found between SGA and exposures to solvents, metals, and miscellaneous chemicals.

Effects of EDC on the risk of POBW<85.

In multivariate analysis, the proportion of infants with POBW<85 among women likely occupationally exposed to pesticides (RRadj 3.72, 95% CI 1.40-9.91) and phthalates 3-fold (RRadj 3.71, 95% CI 1.62-8.51) was higher than that among the women in the reference group. Exposures to ALP was statistically non-significantly associated with increased risk of POBW<85. No association was found between POBW<85 and exposures to PAH, organic solvents, and metals. Exposure to the miscellaneous category had a protective effect.

The most frequently occurring occupations associated with exposure to pesticides with significant adverse effects on fetal growth were veterinary nurses, veterinary assistants, and horticultural trades. The main pesticides encountered were carbamates, organophosphates and pyrethroids. The most prevalent occupations associated with exposure to phthalates with significant adverse effects on fetal growth were hairdressers, beauticians and related occupations and printing machine minders. The phthalates most often encountered were DEHP, BBP, DBP, and DEP. The most prevalent occupations associated with exposure to ALP with significant effect on fetal growth were domestic cleaners, hairdressers and beauticians. The ALP most often encountered were alklylphenols and alkylphenolic

ethoxylates.

Table 3 shows the distribution of pregnancy characteristics of 4142 stratified by likelihood of maternal occupational exposure to EDC during pregnancy. Almost 7.5% of the study cohort were classified as possibly or probably exposed to >1 of 10 classes of EDC. The most common encountered exposures were to organic solvents (4.5%) and ALP (4%) phthalates (1.9%), PAH (1.6%), metals (1.2%), and miscellaneous (1.7%). In general, women who were more likely to be exposed to EDC worked in skilled trades, personal service, elementary occupations, or as machine operators. In addition, their work involved prolonged standing or physical effort and they were more likely to be Causcasian British and less educated.

Discussion

This study provides evidence that maternal occupational exposure during pregnancy to estimated concentrations of EDC - as classified by application of a JEM - is associated with significantly increased risk of impaired fetal growth. In particular, mothers exposed to pesticides were three to five times more likely to have an infant with suboptimal fetal growth as measured by POBW<85 and SGA respectively, and mothers exposed to phthalates were about three times more likely to have a baby with inadequate fetal growth measured by POBW<85. Maternal exposure to ALP was associated with a nonsignificant but increased risk of inadequate fetal growth as measured by SGA and POBW<85.

This study also demonstrated disproportionate exposure to EDC with personal risk factors in women. In general, women who were exposed to EDC were more likely to be Caucasian British, less educated, done work involving prolonged standing or physical effort and worked as skilled trades, personal service, machine operators and elementary occupations.

The study has several strengths primarily due to the large amount and detail of data available. The prospective design minimises recall bias, and selection bias was minimised by the 80% participation rate to the mid-pregnancy. Detailed information was collected about individual maternal characteristics and information obtained on chemical exposures through JEM, which enabled adjustment for potential confounders including adjustment for exposures to individual EDC in order to minimise the effect of possible confounding. The classification of EDC exposures was assessed independently and prior to knowledge of the outcomes by a recently updated JEM developed specifically to assess the association between occupational exposures to EDC and birth outcomes, thus information bias was largely eliminated. We were able to evaluate the effect of several EDC exposures on two different criteria for inadequate fetal growth.

In this study, we used POBW<85 as an indicator of inadequate intrauterine growth that is less dependent on the health of the reference population or the quality of their morphometric data than is percentile position on a birth weight distribution. The method uses optimal rather than expected growth as the standard and reports the ratio of the observed birth dimension to the optimal birth dimension rather than as being above or below a specified position of the population distribution of that dimension, avoiding the problems inherent in the use of percentile position.

The availability of job titles, the detailed information on work tasks or activities routinely performed, type of business and information about when the mother worked during her pregnancy has reduced non-differential misclassification of exposure and enabled a more accurate assessment of occupational exposures compared with studies with access only to job titles.

We validated the job title coding to get a more accurate code for each job title, so the potential for observer bias in the coding of occupational title status was minimised, improving the reliability and validity of the coded job titles. The risk for each category of EDC was estimated, rather than several EDC categories combined, allowing any differences between categories to be observed. Finally, JEM-based assessments of risk of exposures to chemical agents are more reliable than self-reported assessments (17).

A limitation was that individual exposures were not measured. However, Vandenberg et al (44), has reviewed the dose-response between endocrine disrupters and various health outcomes and the possibility of non-monotonic dose-responses. As stated by Vandenberg: "the endocrine system evolved to function when unbound physiologically active ligand (hormones) are present at extremely low doses", "EDCs that mimic natural hormones have been

proposed to follow the same rules and therefore have biological effects at low doses" (44, page 8). Another limitation is that the cells of JEM represent exposure probabilities, which are only a crude measure of exposure, so it needs to be interpreted with caution. Furthermore, the JEM does not consider specific chemicals but only broad groups thereof, and the mechanisms of action can vary between specific chemicals in a group (34). In this study, we reported the specific chemicals identified within each broad group of pesticides, phthalates and alkylphenolic compounds, but it was not possible to distinguish the role of each specific chemicals in their broad groups in the observed lower fetal growth rate. There is also a possibility of overlap between the categories of phthalates and alkyphenolic compounds among exposed mothers, so it was not possible to separate the specific role of each of these chemicals in inadequate fetal growth rate. Finally, too few mothers were exposed to some of EDC such as polychlorinated organic compounds, bisphenol A, and flame-retardants to allow evaluation of their associations with our outcomes. Exposure to the miscellaneous category had a protective effect, but due to small number of exposed people, the CI was very large, (95% CI 0.05-0.60) so the results should be interpreted with caution. Large CI were also observed in the results of occupational groups in table 3. There might be a risk of type 2 errors due to small samples of those exposed to some of EDC. However, for other EDC our results are compatible with those of previous similar studies (4, 16, 17), enhancing their credibility as well as our own.

This study introduces another approach (fetal growth measured by percentage of optimal birth weight) for defining adequacy of growth in assessing the effects of chemical exposures compared to other published studies. To our knowledge, this is the first study to show that the risk of inadequate fetal growth as measured by POBW<85 was significantly elevated following possible or probable maternal occupational exposures to one or more classes of EDC, particularly pesticides and phthalates. A recent study in the Generation R cohort using the same JEM found that occupational exposures to pesticides and phthalates during pregnancy were significantly associated with reduced placental weight and fetal length as estimated by ultrasounds and reduced fetal weight following mother's exposures to phthalates and PAHs (16). Another study from Generation R cohort using the same JEM concluded that maternal occupational exposure to phthalates and pesticides was associated with adverse effects on fertility and pregnancy outcomes (17). A meta-analysis from a European large-scale prospective study using the same JEM also suggests that pregnant women classified as exposed to multiple EDC, including pesticides and phthalates, were at significantly higher risk of term low birth weight newborns in cohorts throughout Europe (4). Our finding in regard to non-significant association between POBW<85 as a measure of fetal growth and maternal exposure to ALP is in line with a recent study in the Generation R cohort using the same JEM in assessing occupational exposure to chemicals and fetal growth as measured by reduced fetal weight estimated from ultrasound-fetometry (16). Our finding about a significant association between maternal exposure to pesticides and SGA is supported by several studies (45-47). However, epidemiological studies on the effect of exposures to endocrine disrupters on pregnancy outcomes are not always consistent, warranting further research into this important topic. For example, the affected occupations associated with exposures to pesticides in this study were those classified as veterinary nurses and horticultural trades and, to phthalates, hairdressers, beauticians, and printing machine minders. The findings in the present study concerning exposure to pesticides and phthalates in hairdressers and agricultural activities and having infants with inadequate fetal growth is in accordance with previous findings (16, 17, 48-50). However, there were some studies in agricultural activities and among hairdressers that show conflicting results (51-54).

There is limited research evaluating the occupational and personal characteristics of women associated with occupational exposures to EDC. Evaluation of the influence of both occupational and personal risk factors (smoking, alcohol consumption, age, marital status, ethnic origin, education, BMI, socio-economic status) would help to improve our understanding of health hazards and develop a comprehensive preventive approach to achieve a longer, healthy working life. Unequal exposure to occupational exposure acting as EDC is an under-recognized risk factor that may play an important role in deriving the higher rates of adverse pregnancy outcomes among those affected populations.

Human development is most vulnerable to toxic substances and endocrine disruption in the early embryonic period. The restricted fetal growth associated with exposure to pesticides and phthalates during pregnancy is an important

public health concern because restricted fetal growth is linked to adverse health later in life such as coronary heart disease, stroke, type 2 diabetes, and hypertension (55). It is therefore important to identify occupation-related risk factors for adverse pregnancy outcomes. Further larger studies are needed to confirm these findings and identify potential targets for prevention. Until then, precautionary prevention and control management of risks to health and safety at the workplace are recommended. In general, the precautions to be taken for the protection of the reproductive health of both women and men will not differ from the safeguarding of all workers. A national priority of supporting research on occupational causes of adverse reproductive outcomes recommended.

Concluding remarks

Consistent with the results of other studies, this prospective birth cohort study provides evidence that occupational exposure to pesticides and phthalates may play a role in the etiology of inadequate fetal growth and SGA infants.

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Conflict of interest

The authors have no conflicts of interest to declare.

Sidebar

This is the first study to show that the risk of inadequate fetal growth as measured by percentage of optimal birth weight (POBW)<85 was elevated following occupational exposures to pesticides and phthalates. Further larger studies are needed to confirm this. Employers should provide workers with adequate education about potential chemical hazards in the workplace to ensure the complete protection of all workers' reproductive health.

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On endocrine disruption at the workplace – how to get from suggestive to conclusive evidence?

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ABSTRACT (ENGLISH)

Bonde explores how to get conclusive evidence on endocrine disruption at the workplace. The health consequences of reproductive hazards at the workplace may be grave for the individual and society. Ensuring a working environment that protects reproductive health must be a high priority. With reference to the precautionary principle, it may be tempting to exclude pregnant women from work that may carry the slightest theoretical risk. But this approach may have strong social and economic consequences for the women who thus do not necessarily benefit from the doubt. Many people need to know more. While experimental studies are important for risk assessment, most rely on epidemiology to address real world occupational exposure scenarios. Epidemiological methods and populations are available, but to ensure progress, a provision of resources is needed to refine assessment of occupational exposure to endocrine disrupting chemicals by ambient air and biological measurements.

FULL TEXT

Headnote

Key terms: birth defect; chemical; chemical exposure; editorial; endocrine disrupting chemical; endocrine disruption; evidence; occupational reproductive hazard; reproductive hazard; women

On endocrine disruption at the workplace - how to get from suggestive to conclusive evidence?

Unusual clusters and outbreaks of reproductive disorders during past decades remind us of the devastating health consequences and human suffering to which exposure to industrial chemicals and pharmaceuticals may give rise. Birth defects caused by gestational exposure to thalidomide, vaginal cancer by diethylstilbestrol, azoospermia by dibromochloropropane, cerebral palsy by methyl mercury, and fetal wasting syndrome by chlorinated biphenyls are all inscribed in medical history as tragic mementos of ignorance and neglect in the past (1).

In parallel with the fast-increasing entrance of women into the workforce, interest in occupational reproductive hazards accelerated in the Nordic countries in the 1970s and 80s. Women working in healthcare, industry, and agriculture are potentially exposed to high levels of chemicals, resulting in possibly substantial risk of toxicity to their unborn child.

Systematic epidemiologic research addressing reproductive hazards at the workplace has fostered thousands of papers from the 1980s to present day. Reports of associations between a large range of exposures and reproductive outcomes spanning infertility, adverse pregnancy outcomes, and childhood cancer and cognitive impairment are abundant. Many studies suggest that in particular organic solvents, pesticides and heavy metals are occupational reproductive hazards, but - with noteworthy exceptions - few specific exposures survive critical systematic review to

become established reproductive toxicants in the workplace (2).

The introduction of the endocrine disruption hypothesis more than 20 years ago has dramatically renewed interest in reproductive toxicity and provided a new framework for research with its focus on a genuine mechanism for toxic effects related to disruption of endogenous hormone homeostasis. Initially it was thought that toxicants interfere with fetal development by mimicking or enhancing effects of natural estradiol (3), but, as evidence accumulated, the hypothesis became much broader. A capacious amount of experimental studies have demonstrated that adverse reproductive outcomes may be related to endocrine disruption of fetal development through xenobiotic interaction with several types of hormone receptors or through interference with synthesis, secretion, transport, metabolism, or degradation of natural hormones (4). If this results in pathologic outcomes, it is not always obvious, and the relevance for human exposure scenarios remain hypothetical (5).

Concern increased as it became evident that virtually all people across the globe host in their bodies not only biopersistent organic pollutants such as DDT and PCBs but also substances with shorter biological half-lives that do not accumulate, such as phthalates (4). The European Chemicals Agency defines endocrine disruptors as chemicals where at least one study has shown not necessarily pathologic or adverse endocrine effects in an intact organism (typically small rodents). The list of such chemicals has become steadily more voluminous and heterogenous and now embraces many of the compounds that have been extensively studied earlier without reference to endocrine disruption - such as organic solvents, cytotoxic drugs, many pesticides, metals, and polyaromatic hydrocarbons (6).

Already in 1999, an editorial advocated for the need to address reproductive toxicity of endocrine disrupting chemicals at the workplace (7), but - in contrast to many studies on exposures in the general environment - to date only few epidemiological studies explicitly addressing endocrine disruption at the workplace have been published (8-14). Therefore, the study by Shirangi and colleagues in this issue of The Scandinavian Journal of Work, Environment and Health is highly welcomed (15). They report associations between occupational exposure to endocrine disrupting chemicals during pregnancy and risk of impaired fetal growth in an English prospective birth cohort, including some 4000 pregnant women. A job exposure matrix (JEM) was used to assess exposure. Substantially elevated relative risks of 3-5 are reported for two of seven classes of endocrine disrupting chemicals - pesticides and phthalates - while no increased risk was found for organic solvents, metals and other exposures. Besides the prospective design, important strengths of this study include a high response and an impressive amount of detailed data on numerous potentially confounding factors, which are accounted for in analyses. The study is also innovative in its use of optimal birth weight in terms of the ratio of observed-to-predicted birth weight as an alternative measure of fetal growth (16). The predicted birth weight was derived from the birthweight distribution among singleton Caucasians without known pathological determinants, such as smoking and birth defects, and was standardized according to gestational age, fetal gender, maternal height, and parity (17). The optimal birth weight measure is less dependent on an appropriate reference population than the traditional small-for-gestational-age measure but neither accounts for ethnicity (almost 30% was of South Asian origin) nor solves the problem of potential collider bias, which is introduced by standardization on gestational age (18).

Although Shirangi et al's study is supported by findings in few earlier studies (9,10), it is reasonable to ask whether we have reached a point where sufficient evidence has accumulated that allows us to provide specific recommendations to work and health authorities. One crucial issue is exposure assessment. Shirangi et al used a qualitative expert-rated JEM tabulating groups of jobs into unlikely, possible, or probable exposure to one or more of ten classes of endocrine disrupting chemicals. JEM may be powerful tools to obtain complete data on exposure without risk of recall bias and at low cost (19, 20) - in particular when a crude exposure assignment based on groups of job titles can be refined by access to individual data on industries and job tasks as in the Shirangi et al study. However, occupational exposure to some endocrine disrupting chemicals, such as phthalates and bisphenol A, has only been quantified by workplace and biological measurement to a very limited extent (21, 22). For example, hairdressers and cosmetologists are the most prevalent occupations exposed to phthalates according to the endocrine disruption JEM, but this finding has not been documented by ambient air, skin or biological samples showing that these occupations do confer an exposure exceeding the background exposure (23, 24). Since

phthalate metabolites are detectable in urine in almost everybody, sources of exposure other than occupational are important. Measurements of occupational exposure and validation of the endocrine disruption JEM by quantitative data is therefore highly warranted. Other occupational exposures, such as pesticides, solvents and metals, are much better documented by workplace measurements, thus their respective JEM may be more valid - in particular when a JEM either provides estimates of exposure to specific compounds or classes of compounds that share mechanism of action, toxic potency and kinetics. The above definition of an endocrine disruptor is far too broad to fulfil this criterion. We need exposure-response data to evaluate causality and provide a basis for regulation and prevention. To obtain exposure-response data, we probably have to get information on specific compounds or group of compounds known to operate by similar mechanism. At present we do not know if current occupational threshold limits for organic solvents, metals and pesticides need to be updated with data on endocrine activity and whether some exposure time windows are more sensitive than others.

Numerous large birth cohorts have been established in Europe over the past 20 years (25), and many of these are designed to examine effects of environmental and occupational exposures (26, 27). It has become feasible to include a whole range of new outcomes that perhaps are more sensitive to endocrine disruption by chemicals during fetal life compared to outcomes observed at birth - for instance premature or delayed puberty (28, 29), infertility in young people (30), and airway disorders (31)

The health consequences of reproductive hazards at the workplace may be grave for the individual and society. Ensuring a working environment that protects reproductive health must be a high priority. With reference to the precautionary principle, it may be tempting to exclude pregnant women from work that may carry the slightest theoretical risk. But this approach may have strong social and economic consequences for the women who thus do not necessarily benefit from the doubt. We need to know more. While experimental studies are important for risk assessment, we rely on epidemiology to address real world occupational exposure scenarios. Epidemiological methods and populations are available, but to ensure progress we need provision of resources to refine assessment of occupational exposure to endocrine disrupting chemicals by ambient air and biological measurements.

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Sidebar

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DETAILS

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Metabolic syndrome – a risk factor for all-cause disability pension: a prospective study based on the Swedish WOLF cohort

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ABSTRACT (ENGLISH)

Objective The aim was to study the impact of metabolic syndrome on the risk for disability pension among Swedish employees. Methods A working population-based prospective cohort [Work, Lipids and Fibrinogen (WOLF) cohort, N=10 803], was linked to national registry records of all-cause disability pension for the period 1992-2013. Occupational health service data included 1992-2009 anthropometric measurements, blood samples, and questionnaires. Metabolic syndrome was defined according to International Diabetes Federation criteria, and risk for any all-cause disability pension was analyzed using Cox proportional hazard regression as hazard ratios (HR) with 95% confidence intervals (CI) adjusted for age, sex and other covariates. Results Of the employees, 17.9% (men 21.5%, women 9.7%) met the criteria for metabolic syndrome. The prevalence of all-cause disability pension was 15.2% in men with metabolic syndrome and 7.5% in men without metabolic syndrome; for women, the corresponding results were 23.2% and 12.7%. After adjustment for sociodemographic factors, health behaviors, work-related factors, diabetes, and obesity, the risk for all-cause disability pension among subjects with metabolic syndrome displayed an HR of 1.37 (95% CI 1.18-1.60). Results were similar for men and women. In a subgroup, further adjustment for chronic diseases resulted in an HR of 1.32 (95% CI 1.04-1.68). Conclusion This study demonstrates an increased risk for all-cause disability pension, even after adjustment for other risk factors, among Swedish employees with metabolic syndrome compared to those without at baseline.

FULL TEXT

Headnote

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Results Of the employees, 17.9% (men 21.5%, women 9.7%) met the criteria for metabolic syndrome. The prevalence of all-cause disability pension was 15.2% in men with metabolic syndrome and 7.5% in men without metabolic syndrome; for women, the corresponding results were 23.2% and 12.7%. After adjustment for sociodemographic factors, health behaviors, work-related factors, diabetes, and obesity, the risk for all-cause disability pension among subjects with metabolic syndrome displayed an HR of 1.37 (95% CI 1.18-1.60). Results were similar for men and women. In a subgroup, further adjustment for chronic diseases resulted in an HR of 1.32 (95% CI 1.04-1.68).

Conclusion This study demonstrates an increased risk for all-cause disability pension, even after adjustment for other risk factors, among Swedish employees with metabolic syndrome compared to those without at baseline.

Key terms abdominal obesity; blood lipid; employee; glucose; hypertension; longitudinal; Sweden; work ability.

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In 1998, the World Health Organization (WHO) defined simultaneous occurrence of several cardiovascular risk factors - insulin resistance, dyslipidemia, hypertension, obesity or central obesity (increased waist circumference) - as metabolic syndrome (MetS) (1, 2). Several definitions of MetS are valid, each focusing on different metabolic factors in the syndrome. The prevalence of MetS in different European and North American populations is estimated to be 9.4-23.8% depending on the criteria definition of MetS and the observed population (3, 4). Diabetes mellitus type 2 (DM2) and MetS are separate disorders but could both be associated with cardiovascular comorbidity as they share similar metabolic risk factors; there are also indications that MetS in itself could be a precursor of cardiovascular disease and DM2 (5-7). Published data describing work ability and disability pension in diabetic patients in the workforce are numerous (8-11) but there is considerably less, if any, knowledge about the impact of MetS on work ability and the risk for disability pension. Of relevance is a study by Lam &LeRoith (12) describing the

multi-organ effects related to MetS, with insulin resistance playing a key role in the development of MetS and another by Taylor &MacQueen (13), who in 2007 described the effect on cognitive performance in MetS.
The concept of work disability encompasses several areas of science but its endpoint - disability pension - is a statutory or insurance-based construct that depends on identifiable medical diagnoses relating to biological characteristics of an individual. Medically motivated impairments lead to an incapacity of the individual to perform allotted work tasks and maintain gainful full-time employment until retirement age (14). Work ability can be evaluated with prognostic tools such as the Work Ability Index (WAI), but there is a lack of methods for assessing work disability in epidemiological studies (15). The possibility to predict the risk for disability pension has been described in a follow-up study of work-related psychosocial demands (16). Sustained work disability may eventually lead to disability pension, which can be monitored and evaluated using social registry data on disability pension (17).
The Work, Lipids and Fibrinogen (WOLF) cohort is well studied (18). The WOLF surveys are based on questionnaires, clinical examinations, anthropometric measurements, and blood sampling among employees in different branches of work and different parts of Sweden during 1992-2009 and, therefore, provides valuable data for the present study (www.wolfstudy.se).
The aim of this study was to explore the impact of MetS on the probability of disability pension among employees in the Swedish workforce.

Methods

Design and study population

We conducted a working population-based prospective cohort study using data collected since 1992 from the WOLF cohort surveys. Study subjects participated in an extensive set of WOLF surveys comprising anthropometric measurements and blood samples at baseline and questionnaires administered on one to three occasions during 1992-1997 and 2000-2003, with a follow-up survey in 2009. The study subjects were 15-64 years of age and were recruited from 36 occupational health service units and employed in 159 different occupations (according to the Nordic Classification of Occupations (19) in approximately 60 companies located in Stockholm county and in the northern Swedish counties of Västernorrland and Jämtland. Workers in the enrolled companies were invited to participate, but subjects on long-term leave from their workplace were not included. Participating workers were employed in transportation, industry, public administration, telecommunications, sales, teaching, construction and finance.
Clinical examination at the occupational health service units included standardized measurement of blood pressure (BP) and measurements of length, weight, and waist and hip circumference. Sampling of fasting blood glucose (FPG) and blood lipids followed standardized procedures and the blood samples were analyzed at an accredited laboratory. The WOLF survey questionnaires addressed work and health conditions, socio-demographic status, and job strain and other psychosocial factors. The questionnaires also included questions on tobacco and alcohol use, exercise habits, and cardiovascular risk factors.
For 10 803 study subjects derived from the WOLF cohort, complete information on parameters regarding MetS was available. In the northern Swedish counties, 2013 subjects completed a second clinical investigation. All participants in earlier WOLF surveys were invited to respond to the 2009 follow-up survey, 6352 subjects answered and thus formed a sub-group. The final 2009 survey also included questions regarding specific chronic diseases.

Definitions

Disability pension. We chose to use any all-cause disability pension (full- or part-time) as a proxy for work disability. The WOLF cohort data were matched with de-identified data from an official registry, the Longitudinal Integrations Database for Health Insurance and Labor Market Studies (LISA) registry, published by Statistics Sweden (SCB). The LISA register is updated yearly and comprises aggregated socio-economic and demographic data, derived from different registers, on all citizens aged >16 years living in Sweden (www.scb. se). The LISA database is enabled by the use of unique personal identification numbers (PIN) (20). In this study, the matching LISA data cover the years 1990-2013, and the subjects were followed regarding all-cause disability pension from their first year in the study until the last year of the follow-up. Statistics Sweden carried out the merging of data for all subjects in the WOLF

cohort with corresponding data from the LISA database. The merged data for the study period 1990-2013 were then anonymized (ie, the PIN were removed) and sent back for further analysis.

Metabolic syndrome. Of the different definitions of MetS, we preferred using the definition given in 2005 by the International Diabetes Federation (IDF) (www.idf.org) (21), for analysis of the WOLF survey data. The IDF criteria for the MetS require the mandatory presence of central obesity (a circumferential waist measurement of >94 cm for men and >80 cm for women) and the presence of >2 of 4 of the following criteria: (i) raised FPG >100 mg/dL (5.6 mmol/L) or diagnosed diabetes; (ii) raised BP, with systolic BP >130 or diastolic BP >85 mmHg, or treatment for diagnosed hypertension; (iii) raised triglycerides >150 mg/dL (1.7 mmol/L) or pharmaceutical treatment for blood lipids; and (iv) reduced level of high-density lipoprotein cholesterol (HDL-C), of <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females, or pharmaceutical treatment for blood lipids. Information on use of pharmaceutical treatment and diabetes diagnosis was derived from the questionnaires.

The study population was divided into two groups, those with MetS at baseline or at the second clinical investigation (MetS group) and those without metabolic syndrome (non-MetS group). If a study subject met the MetS criteria at the second medical investigation, this occasion constituted baseline in the further analyses.

Socio-demographic factors. Region was classified according to employment location as 0=Stockholm county, and 1=the counties of Västernorrland and Jämtland. Job level was derived from the LISA registry, and 10-13 occupationally based socio-economic groups (the division of groups was changed by the SCB during the follow-up time) were categorized into three levels. In the final analyses, levels 2 and 3 were combined (as their results were similar) and compared with the highest job level (level 1). Classification of education was done based on the baseline questionnaire, where one item covered nine types of school as well as university education. Educational level was divided into low (6-9 years) and high (university or similar), both of which were compared with medium-length education. Civil status was derived from the baseline questionnaire, with four response alternatives (married or cohabiting/unmarried/ divorced/widowed) classified as 0=married or cohabiting, while 1=single.

Health behaviors. Smoking habits were derived from items in the baseline questionnaire and categorized as ever-smoking or not. Physical exercise was assessed from the baseline questionnaire item "How often do you exercise?" The item had four response alternatives (never/rarely/sometimes/regularly), with "never" and "rarely" classified as low exercise level and "regularly" as high exercise level. "Sometimes" was used as the reference value.

Work-related factors. Level of control was classified according to the demand-control model (22) with five items on demand and six on decision latitude (control) derived from the baseline questionnaire. The items had four response alternatives (yes, often/yes, sometimes/ no, rarely/no, never) scoring 1-4 points. The sum was calculated, and the median was used to classify high demand and low control, respectively, as 1. High strain (defined as having both high demand and low control) was also tested but it was low control that demonstrated the strongest association with disability pension and that was therefore used in the analyses. Physical workload at work was classified from the baseline questionnaire, the subjects were asked to assess how physically demanding their work was on a scale of 0=very, very light to 14=very, very strenuous. We classified 0-3 as low and 9-14 as high physical workload and compared them with moderate physical workload of 4-8.

Metabolic syndrome-related factors. Diabetes was derived from the baseline questionnaire question "Do you have diabetes?" (yes/no). Body mass index (BMI) was calculated from baseline measurements of weight and length. A BMI >30 was defined as obesity (23).

Chronic diseases. From the questionnaire administered at follow-up in 2009, the item "Do you have or have you had any physician-diagnosed diseases or disorders during the last 5 years?" - with specific disease alternatives and three answer alternatives for each disease/disorder (no, not at all/not now, but during the last 5 years / yes, now) - was used to classify "no, not at all" as 0 and the other two responses as 1. These diseases were included in the analysis as they could affect work ability: rheumatologic diseases, musculoskeletal disorders, cardiovascular diseases, psychiatric disease, and asthma/ obstructive lung disease.

Statistical analysis

Frequencies of baseline characteristics, such as MetS criteria and potential risk factors (covariates) for all-cause

disability pension used in the analyses, were calculated for all subjects, and for men and women in the MetS and non-MetS group, respectively. For continuous variables, mean values with standard deviations (SD) were calculated. Time at risk (in person-years) was calculated from entry into the study between 1992-2003 (94% of the subjects were included at the end of 1997) until the end of follow-up. End of follow up was the first occurring event of: (i) disability pension, (ii) death, (iii) unavailable in the LISA registry (not registered as a resident in Sweden at the last day of the year, 2.5%), (iv) retirement at age 65 or before, or (v) the end of the study period in 2013. Incidence rates per 1000 person-years, with 95% confidence intervals (CI), were calculated for first occurrence of all-cause disability pension during time at risk for men and women in the MetS and non-MetS groups, respectively. The risk for all-cause disability pension due to MetS was analyzed using Cox proportional hazard regression in a base model (model 1) adjusting for both age (in years) at study entry and sex, yielding hazard ratios (HR) with 95% CI. Further, three models were analyzed adjusting also for three different sets of covariates: model 2 - base factors and socio-demographic factors (region, job level, education level - low and high compared with medium-length education - and civil status), model 3 - base factors and health behaviors (ever-smoking, physical exercise - low and high exercise level, compared with exercising "sometimes") and model 4 - base factors and work-related factors (low control in the demand-control model, physical workload at work - low and high workload compared with moderate physical workload). In model 5 (non-MetS-related factors), all three sets of covariates were analyzed together with the base model. In model 6, the base model was analyzed together with the MetS-related factors diabetes and obesity. The final model, model 7, adjusted for all above-mentioned factors.

All covariates were significant when analyzed in models 2-4, and most but not all were significant in the final adjusted model. All covariates but one (region) were separately significant in the base model.

Risk consumption of alcohol, estimated from the baseline questionnaire, was tested with the base model but HR was not increased and it did not change the estimate of MetS and therefore it was omitted. The item "ever shift work" (from the baseline questionnaire) tested with the base model was significantly increased but when tested with the set of work-related factors gave a P-value of 0.44 and was therefore omitted. The seven models were also performed for men and women separately. The same calculations were done for the subgroup (N=6352).

The SAS program version 9.4 (SAS Institute, Cary, NC, USA) was used for the analyses. For Cox regressions, the PHREG procedure in SAS was applied, and this was also used when proportionality of hazards was tested using log-log survival functions.

The Review board of the Regional Ethics Committee at the University of Gothenburg approved the study (082-15, 26 March 2015).

Results

The entire study population consisted of 10 803 employed subjects (69.5% men, 30.5% women). Of these, 17.9% (21.5% of men, 9.7% of women) met the IDF criteria for MetS. Baseline characteristics and covariates of the study subjects are presented in table 1. Of the study population 41.9% had central obesity at the start of study, and of these 25.5% were obese (BMI>30). Of those with MetS, 65.4% were not obese (BMI>30). In the non-MetS group, 27.8% of men and 32.1% of women had a waist circumference exceeding the IDF criteria but did not fulfill the other criteria required for definition of MetS. Elevated FPG levels or treatment for diabetes were evident in 5.8% of subjects in the non-MetS group, but only 0.8% of them had a diabetes diagnosis.

The results from baseline measurements and blood samples for study subjects with or without MetS are presented in table 2. Age at inclusion was about 6 years lower in the non-MetS group (P<0.05). Measurements and blood samples displayed elevated levels of triglycerides, FPG and systolic and diastolic BP, and lower levels of HDL-C in the MetS group compared with the non-MetS group, as expected.

Table 3 illustrates the proportion of subjects receiving all-cause disability pension as well as the mean age at disability pension and the incidence rate of allcause disability pension. Total person-years at risk were 149 938, with a mean of 14.4 (SD 5.3) years for the nonMetS group and 11.4 (SD 5.5) years for the MetS group (data not shown). All-cause disability pension occurred in 7.5% of men in the non-MetS group compared with 15.2% in the MetS group; for women, the corresponding figures were 12.7% and 23.2%, respectively. The incidence rate of all-cause

disability pension for subjects in the non-MetS group was 6.4 per 1000 person-years and 14.5 for subjects with MetS. Mean age at all-cause disability pension was similar between men and women in the MetS group but not in the non-MetS group. The mean age at all-cause disability pension for all subjects in the study was 55.4 years of age (SD 7.5).

Table 4 displays the risk of all-cause disability pension among subjects with MetS, with adjustment for potential explanatory and mediating factors at baseline. After adjustment for all covariates the final HR for allcause disability pension in the MetS group subjects was 1.37 (95% CI 1.18-1.60) compared with the non-MetS group. Socio-demographic factors, health behaviors and work-related factors all influenced the risk for all-cause disability pension. However, the increased risk for allcause disability pension remained elevated in the MetS group when adjusting for these factors. The final HR for women will be 1.34 (95% CI 1.01-1.79) if we exclude the non-significant factors (P>0.20) in model 7 (data not shown).

With adjustment for diabetes and obesity in the base model, the HR for all-cause disability pension in the MetS group was 1.41 (95% CI 1.22-1.63). The risk for all-cause disability pension when having diabetes was 2.10 (95% CI 1.56-2.82) in this model (data not shown). The results were similar for men and women in all combinations of chosen covariates in the specified models.

The subgroup answering the follow-up questionnaire in 2009 had similar baseline characteristics and covariates as the whole study population (data not shown). In the base model for the subgroup the risk for all-cause disability pension was 1.84 (95% CI 1.53-2.21) in the MetS group. After adjusting for reported chronic diseases, HR was 1.52 (95% CI 1.23-1.89) and after adjusting for chronic diseases and all other covariates, HR was 1.32 (95% CI 1.04-1.68). For women in the MetS group, the risk for all-cause disability pension was non-significant when adjusting for reported chronic diseases in the base model, HR 1.21 (95% CI 0.81-1.81). Among men the corresponding analysis yielded an HR of 1.69 (95% CI 1.30-2.19).

Discussion

The main finding in this working life prospective study is that Swedish employees with MetS had a considerably elevated risk of all-cause disability pension compared with employees without MetS. The risk for all-cause disability pension remained elevated after adjustment for other covariates such as age at inclusion in the study, sex, socio-demographic factors, health behaviors, workrelated factors including the demand-control model, and the MetS-related factors diabetes and obesity. To our knowledge, this is the first study on this topic.

The presence of MetS or non-MetS was based on an internationally recognized definition of MetS, the IDF criteria, which is clinically useful (21). Measurements of waist circumference, BMI, BP, blood samples of FPG and blood lipids are easily accessible in everyday medical practice. The IDF criteria also allow comparison with the results from other studies using the same or comparable MetS criteria. This study found similar results, concerning MetS, as reported in previous studies in which the prevalence was estimated to be about 10-20%, depending on the criteria definition for MetS, as well as the population and the subjects' age (3).

Our study is based on a long-term follow-up of a representative cohort of employed men and women of normal working age, recruited from a variety of occupations at workplaces located in three counties in Sweden. Data collection in the WOLF surveys was based on self-administered questionnaires and closely supervised by local occupational health service personnel who also performed standardized measurements and blood sampling. The assessment of MetS was based on at least one health examination carried out in the WOLF cohort at each subject's entrance year into the study. The health examination included the necessary measurements and blood samples to confirm or reject the MetS diagnosis. The assessment of self-reported chronic disease or conditions of importance was first established in the final survey questionnaire in 2009. The quality of data in the LISA database depends on the registries that supply data to the database; and the linkage between these registers is by use of the individual PIN code as a common denominator (20).

Since the 2009 WOLF survey did not comprise measurements and blood sampling, the true prevalence of MetS in the cohort at the end of the study period is not known even though this study shows that one-third of subjects in the non-MetS group met the prerequisite for MetS, increased waist circumference, but did not fulfill the other MetS

criteria at baseline.
The main focus in this study was working employees; those on long-term leave from their workplace were excluded. The size of the total workforce is therefore not known, which may have led to a possible underestimation of the risk of all-cause disability pension.
The complex mechanisms in MetS leading to reduced work ability and, eventually, the loss of work ability are not fully understood. Insulin resistance, visceral adiposity and atherogenic dyslipidemia are known interrelated features sharing common mediators and pathophysi- ological mechanisms (2). We therefore wanted to adjust for diabetes and obesity in our analyses, but that did not account for the risk for disability pension among subjects with MetS.
Another aspect of work ability is the cognitive requirements in modern working life. In a complex working life, cognitive demands are crucial for productivity and could therefore be affected by the complex neuroanatomical and neuroendocrine changes inherent in MetS, as described by Taylor &MacQueen (13).
The chain of action explaining why MetS leads to an elevated risk of disability pension is to some extent understood concerning risk factors and mechanisms, but the complex underlying causes of loss of work ability are not known.
Implications
In this study, we found an overall elevated risk of allcause disability pension among study subjects with MetS. The implications of this new knowledge are that it could, through screening of groups with at least one risk factor, contribute to an awareness of the importance of early medical recognition of MetS, enabling necessary lifestyle changes, medical treatment and adequate intervention at the workplace in order to maintain work ability throughout the working life.
Contrary to MetS, DM2 is a well-known identifiable condition, which is often recognized early and monitored and medically treated, and whose impact on work ability and risk for disability pension is described in numerous studies (8-10). In this study, the number of subjects with MetS by far exceeded the number of subjects with diagnosed DM2; however, compared with DM2, MetS is much less of a diagnosed and medically treated entity. This is also understood by the fact that MetS is not recognized as a definable unique International Classification of Diseases, 10th revision (ICD-10), diagnostic code; although the definition "metabolic syndrome" was established by WHO already in 1998 (1, 24). Today the risk factors related to metabolic disorders - obesity, abdominal obesity, blood lipid disturbances, hypertension, and insulin resistance with diabetic and non-diabetic hyper glycaemia - are often separately diagnosed and medically treated. A patient with hypertension or lipid disturbances is not routinely checked for waist circumference, and vice versa, but measurement of waist circumference is mandatory in establishing the entity of MetS, using the IDF criteria. These shortcomings complicate systematic preventive actions. The lack of a recognized diagnostic entity with an ICD-10 diagnostic code also implies that subjects with unidentified MetS are at risk of being without proper lifestyle interventions and medical care for the combined risk burden of the syndrome and also of work disability, and may eventually end their working life at an earlier stage, with a disability pension, as illustrated in this study.
Concluding remarks
Many factors are involved in the risk of all-cause disability pension but the presence of MetS was an independent and significant risk factor in this study.
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Sidebar
In this prospective cohort study, Swedish employees with metabolic syndrome had an increased risk for all-cause disability pension, even after adjustment for other risk factors, compared with employees without metabolic syndrome. This implies the need for early recognition and treatment of the metabolic syndrome in order to achieve and maintain work ability throughout the working life.
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DETAILS

Subject:	Population; Insulin resistance; Diabetes; Womens health; Occupational health care services; Risk factors; Questionnaires; Chronic illnesses; Metabolic disorders; Health hazards; Women; Lipids; Statistical analysis; Risk analysis; Men; Confidence intervals; Pharmaceuticals; Subgroups; Diabetes mellitus; Hypertension; Sociodemographics; Obesity; Occupational health; Fibrinogen; Glucose; Metabolic syndrome; Regression analysis; Health services; Education; Health risks; Personal identification numbers; Employment; Employees; Disability pensions
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The effects of the number of consecutive night shifts on sleep duration and quality

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ABSTRACT (ENGLISH)

Objectives The organization of night shift work affects sleep duration and quality. The aim of this study was to investigate the effects of the number of consecutive night shifts on sleep duration and quality among police officers with night shift work as part of their normal schedule. Methods This quasi-experimental, within-subject crossover study included 73 police officers. All participants performed three work schedules: two, four and seven consecutive night shifts followed by the same number of recovery days, ie, day work or days off (2+2, 4+4, and 7+7). Sleep assessed through sleep diaries and actigraphy after all night shifts and recovery days (totaling 26 days) was compared by use of repeated measures analysis. Results Participants experienced shorter sleep duration (with and without naps), more premature awakening, less difficulty falling asleep, and more non-refreshing sleep after night shifts compared with recovery days. Sleep duration and quality did not change with increasing number of consecutive night shifts. Sleep was shorter and of poorer quality after the last night shift in the 2+2 and 4+4 work schedule compared with the second and fourth night shift, respectively, in the 7+7 schedule. Conclusion Sleep duration was reduced after night shift work and did not increase with more consecutive night shifts, which leads to accumulated sleep debt. Sleep duration was shortest and sleep quality was poorest after the last night shift in a series of night shifts.

FULL TEXT

Headnote

Objectives The organization of night shift work affects sleep duration and quality. The aim of this study was to investigate the effects of the number of consecutive night shifts on sleep duration and quality among police officers with night shift work as part of their normal schedule.

Methods This quasi-experimental, within-subject crossover study included 73 police officers. All participants performed three work schedules: two, four and seven consecutive night shifts followed by the same number of recovery days, ie, day work or days off (2+2, 4+4, and 7+7). Sleep assessed through sleep diaries and actigraphy after all night shifts and recovery days (totaling 26 days) was compared by use of repeated measures analysis.

Results Participants experienced shorter sleep duration (with and without naps), more premature awakening, less difficulty falling asleep, and more non-refreshing sleep after night shifts compared with recovery days. Sleep duration and quality did not change with increasing number of consecutive night shifts. Sleep was shorter and of poorer quality after the last night shift in the 2+2 and 4+4 work schedule compared with the second and fourth night shift, respectively, in the 7+7 schedule.

Conclusion Sleep duration was reduced after night shift work and did not increase with more consecutive night shifts, which leads to accumulated sleep debt. Sleep duration was shortest and sleep quality was poorest after the last night shift in a series of night shifts.

Key terms fast rotation; night shift work; night worker; shift work; shift worker; sleep quality; slow rotation.

It is well established that night shift work causes reduced and disturbed sleep. Night shift workers report premature awakenings and insufficient sleep, yet ~50% of individuals experience a spontaneous and effortless sleep termination (1, 2). The organization of night shifts may influence the effect of night shift work on sleep. For example, a slowly backward-rotating work schedule (eg, changing from night to evening to day shifts with seven consecutive shifts) has been found to be associated with more impairments of sleep than a fast forward-rotating work schedule (eg, changing from day to evening to night shifts with two to four consecutive shifts) (2-4). Nevertheless, only a few intervention studies have investigated the isolated effect of changing the speed of rotation (5, 6). On the one hand, these studies suggest that fast rotation, ie, few consecutive night shifts, is associated with fewer sleep disturbances

and difficulties (5, 6). This would favor night shift work schedules with few consecutive night shifts. On the other hand, studies have shown that there is some adaptation of biological rhythms to sleeping during the day leading to gradual improvement of sleep with increasing consecutive night shifts (7). This would favor night shift work schedules with slow rotations, ie, more consecutive night shifts.

Short sleep duration and poor sleep quality has, in studies with longitudinal designs, been associated with higher risk of diabetes (8) and cardiovascular disease (9, 10) and may serve as a mechanism linking night shift work to increased risk of injuries and accidents (11) as well as chronic disease (12-16). When night shift work is inevitable, such as in the hospital sector and police force, it is essential to find the best way of organizing night shift work to minimize the impact of night shift work on health. To reduce unhealthy consequences of night shift work, it has been recommended to reduce the number of consecutive night shifts in order to reduce circadian disruption (17). Yet, it is, unclear what the optimal number of consecutive night shifts is when considering sleep duration and different aspects of sleep quality.

The overall aim was to contribute to the knowledge about how to optimally organize night shift work in order to reduce sleep deprivation and negative health consequences. We therefore investigated the effects of the number of consecutive night shifts on sleep duration and quality among police officers with night shift work as part of their regular schedule. During the study period, each participant was enrolled in three different work schedules: two, four and seven consecutive night shifts followed by the same number of recovery days, ie, day work or days off (hereafter: 2+2, 4+4, and 7+7). The main aim of the study was fulfilled by answering the following questions: (i) Is sleep duration shorter and sleep quality poorer after night shifts compared with recovery days (independent of work schedule)? (ii) Does sleep duration increase and sleep quality improve with an increasing number of consecutive night shifts or recovery days? (iii) Is sleep duration shorter and sleep quality poorer after the last night shift in a series of night shifts regardless of the number of previous night shifts?

Methods

This paper presents results from the project "In the Middle of the Night". The National Committee on Health Research Ethics in Denmark approved the study (protocol number H-4-2012-155).

Design

Conducted with a quasi-experimental, within-subject crossover design, the study exposed the participants to three different work schedules: two night shifts followed by two recovery days (2+2), four night shifts followed by four recovery days (4+4), and seven night shifts followed by seven recovery days (7+7). The term recovery day were used for days that allowed sleep at night and included both day shifts (31%) and days off (69%). Day shifts were typically 07:00-15:00 (we allowed day shifts to end as late as 18:00) and night shifts were typically 23:00-07:00 (we allowed the start of the night shifts to vary between 22:00 and 00:00). The participants did not work any night shifts during the seven days preceding the start of the three different work schedules.

Data were collected either in the period April-June 2013 or September-November 2013. Daylight saving time began March 27 and ended October 27 in 2013. None of the participants had data collection on these two dates and only three participants collected data after the end of daylight saving time. The three different work schedules lasted 26 days in total, and they could be distributed over no longer than three months. The order of the three different work schedules occurred in the order that suited the person in charge of the personnel-on-duty planning. This person was instructed to mix the different work schedules so they occurred in different orders and to let the different work schedules in the study begin on different weekdays. In accordance with the usual way of scheduling the shifts, the starting date of the different work schedules was planned so that it also suited the individual employee. This meant that of the 64 participants who performed all three work schedules, 18 (28%) started with the 2+2, 17 (27%) with the 4+4 and 29 (45%) with the 7+7.

Recruitment procedure and study population

Throughout all phases of the study, there was intensive collaboration and strong support from both the management in the Danish police and employee representatives from the labor union. We recruited participants from the five police districts in Zeeland, Denmark. The inclusion criteria were that the participants had to be non-smoking male

police officers with night shifts as a part of their regular schedule, but not working permanent night. The officers use self-rostering to plan their normal schedules. They are therefore not regular and may vary from person to person. In most cases, they include up to four consecutive night shifts, although seven consecutive shifts were in some cases allowed if the officer requested it. Before recruitment began, information meetings were held for the leaders, the people responsible for personnel-on-duty planning, and employee representatives. All districts were also offered an initial information meeting for potential participants, which were accepted by two police districts. Thereafter, an e-mail was sent to all potential participants in all districts with an invitation to participate in the study. A total of 121 police officers showed interest in participating in the study. Of these, a total of 73 received individual, detailed information about the project either face-to-face or on the phone and completed at least one of the three work schedules, and 64 completed all three work schedules. Reasons for dropping out were holidays or other fixed duties, change to a job without night shift work or family considerations.

Questionnaire

The participants completed a background questionnaire before starting their first work schedule in the study. From the questionnaire, we obtained information about tenure within the police force, night shift work experience, physical activity, self-rated overall health, general job satisfaction, and diurnal type.

Sleep dairies

All participants scored their sleep quality upon awakening from their primary sleep on all 26 data collection days. Primary sleep was defined as the first sleep episode after the night shift or as sleep during the night after recovery days. Sleep was scored using a modified version of the Karolínska Sleep Diary (KSD) (18, 19). In total, seven items were used: premature awakening, difficulty falling asleep, difficulty awakening, nonrefreshing sleep, disturbed sleep, number of awakenings, and overall sleep quality. Number of awakenings was given a 1-5 score (0 awakenings=1, >4 awakenings=5). All other items were scored on a 5-point scale, with higher scores representing poorer sleep. In their sleep dairies, participants also noted the number, timing, and duration of naps.

Actigraphy

Actiwatches (ActiGraph wGT3X-BT from ActiGraph FL, USA) were worn on the non-dominant wrist during all 26 data collection days. Data were collected with a sampling rate of 30 Hz and 1-minute epochs were used to score sleep. Data were analyzed with ActiGraph Sleep Analysis (ActiGraph, FL, USA). In and out of bed times were taken from the sleep dairies. The following variables were extracted: primary sleep duration (PSD), total sleep time per day including naps (TST), and sleep efficiency.

Statistical analysis

Unless otherwise stated, we performed repeated measures ANOVA using the PROC MIXED procedure with a random intercept for each individual to account for within subject variation (20). Separate analyses were made with ten parameters of sleep duration and quality as continuous outcomes: premature awakening, difficulty falling asleep, difficulty awakening, non-refreshing sleep, disturbed sleep, number of awakenings and sleep quality from sleep diaries as well as PSD, TST and sleep efficiency from actigraphy. The MIXED procedure has the advantage that it can accommodate data that are missing at random. Due to multiple statistical testing, results were considered to be statistically significant at $P<0.001$.

In the first set of analyses, sleep duration and quality after night shifts were compared with sleep duration and quality on recovery days independent of work schedule using the full dataset (all night shifts and recovery days, totaling 26 days) (research question 1). In the second set of analyses, repeated measures linear regression analysis was used to evaluate if there was a change in sleep duration and quality with increasing number of consecutive night shifts or recovery days (research question 2). These analyses were performed separately for night shifts and recovery days. In this set of analyses, the last night shift and the last recovery day of each work schedule were excluded, ie, the second night shift and the second recovery day in 2+2 and the fourth night shift and the fourth recovery day in 4+4 etc. This was done because (later) analyses showed that sleeping behavior was different after the last night shift, and including these data in the analysis could mislead the interpretation of the effect of number of consecutive of night shifts on sleep. In the third set of analyses, we investigated if sleep duration and quality after the last night shift

in a series of night shifts differed from other days (research question 3). We compared sleep duration and quality after the last night shift in the 2+2 and 4+4 work schedule with the second and fourth night shift, respectively, in the 7+7 work schedule (reference). All statistical analyses were done in the statistical software SAS for Windows 9.4 (TS level 1M3, SAS Institute, Cary, NC, USA).

Results

The participants were aged 25-62 years with a mean age of 38 years; 22% had <3 years of night shift work experience, 38% had 3-10 years of night shift work experience, and 40% had >10 years of night shift work experience. Most participants rated their health excellent (31%) or very good (47%) and 78% were moderately or highly physically active in their leisure time (table 1). Of the participants, <9% worked during the day on the first recovery day after a series of night shifts. On average, 38% of the recovery days (excluding the first recovery day) were (daytime) work days and 62% were days off. Of the 2+2 work schedule recovery days, 13% were (daytime) work days, whereas 35% and 34% of recovery days in the 4+4 and 7+7 schedules, respectively, were (daytime) work days. The average awakening time was 06:48 hours on recovery days with work and 07:25 hours on recovery days without work.

Figure 1 illustrates PSD, TST, premature awakening, difficulty falling asleep, difficulty awakening, and non-refreshing sleep for all 26 days in the 2+2, 4+4, and 7+7 schedules. Data for all variables of sleep duration and sleep quality for all 26 days in the three different work schedules are shown in the supplementary material (www.sjweh.fi/show_abstract.php?abstract_id=3885 table S1). PSD was 01:32 [standard deviation (SD) 00:04] hours and TST was 01:04 (SD 00:04) hours shorter after night shifts compared with recovery days (table 2) (research question 1). The officers also reported more premature awakening, less difficulty falling asleep and more non-refreshing sleep after night shifts compared with recovery days (table 2). Table 2 also shows the estimated slope in sleep duration and quality with an increasing number of consecutive night shifts or recov- ery days, respectively (research question 2). Sleep duration and quality did not change with increasing number of consecutive night shifts. In contrast, difficulty falling asleep, difficulty awakening, non-refreshing sleep, disturbed sleep, and number of awakenings decreased with more consecutive recovery days (P<0.001).

Participants had shorter PSD (B= -01:01, SD 0:13 hours) and TST (B= -00:53, SD 0:14 hours) after the last night shift in the 2+2 work schedule compared with the second night shift in the 7+7 work schedule (research question 3). Participants also experienced more difficulty awakening (B=00.58, SD 00.13 hours) and more non-refreshing sleep (B=00.51, SD 00.11 hours) after the last night shift in the 2+2 work schedule compared with the second night shift in the 7+7 work schedule. Similar differences were observed after the last night shift in the 4+4 schedule compared with the fourth night shift in the 7+7 work schedule (table 3). There were no other statistically significant differences in this set of analyses. The cumulative sleep debt can be estimated as: (number of consecutive nights) x (difference between TST on night shift and recovery days) + (the difference between the last night shift in a series and other night shifts). As an example, the estimate for two consecutive night shifts is: two consecutive night shifts x 01:04 hours per night shift + 00:53 hours equaling 03:01 hours. Thus, the estimated cumulative sleep loss is 03:01, 05:09, and 08:21 hours after two, four and seven consecutive night shifts, respectively.

Discussion

In this study of 73 police officers working 2+2, 4+4 and 7+7 work schedules, we found that participants experienced shorter sleep duration (with and without naps), more premature awakening, less difficulty falling asleep, and more non-refreshing sleep after night shifts compared with recovery days. Sleep duration and quality did not change with increasing number of consecutive night shifts, but reports of difficulty falling asleep, difficulty awakening, non-refreshing sleep, and disturbed sleep decreased with increasing number of consecutive recovery days. Sleep was shorter and of poorer quality after the last night shift in a series of night shifts.

It has been argued that more consecutive night shifts cause adaptation of circadian rhythms leading to better and longer sleep during the day eg, among employees on oil rigs in the North Sea (7). In contrast, the results of the present study clearly showed that sleep duration and quality did not change with number of consecutive night shifts among night shift workers. Therefore, adaptation of sleep duration did not occur, and the participants slept at least

one hour less after a night shift than on recovery days even after six consecutive night shifts.
We have previously shown results regarding diurnal rhythms of hormones from the same study (21). The rhythm of melatonin was suppressed and cortisol was phase delayed with increasing number of consecutive night shifts, and after six consecutive night shifts there was not a full adaptation of the diurnal rhythms to day time sleep. In total, neither the diurnal rhythms of hormones nor the sleep duration fully adapted to night shifts. Accordingly, the police officers build up sleep debt with more consecutive night shifts. While alertness appears rather robust against small curtailments of sleep (1), experimental laboratory studies have shown that as little as two hours of daily sleep restriction over two weeks leads to accumulative decline in cognitive performance (22).
Previous studies have found that few consecutive night shifts (as part of a fast forward-rotating schedules) were associated with fewer sleep disturbances and difficulties than more consecutive night shifts (as part of a slowly backwards-rotating schedules) (2-6). In the present study, we specifically studied the effects of the number of consecutive night shifts without changing the direction of rotation, and found that participants had particularly short and poor sleep after the last night shift after both two and four consecutive shifts. Particularly, the participants reported more difficulty awakening and more non-refreshing sleep after the last night shift in a series of night shifts. This finding is in accordance with the notion that shift workers shorten their sleep after the last night shift in order to change back to night-time sleep. Thus, if an employee has to cover a fixed number of night shifts, the employee will have more "last night shifts" in a schedule with few consecutive night shifts compared with a schedule with more consecutive night shifts. Therefore, a schedule with few consecutive night shifts (fast rotation) implies more days with poor sleep compared with a schedule with more consecutive night shifts.
Our findings - that night shift workers experience shorter sleep and find it easier to fall asleep and wake up although not feeling refreshed after night shift work - are congruent with previous studies (1, 2). The total time awake when working the first night shift is often 20-22 hours or more, whereas it is 16-18 hours for a worker with permanent day work. Thus, the sleep pressure is higher after the first night shift, which may explain why participants experience less difficulty falling asleep after a night shift compared with a recovery day. Furthermore, night workers sleep during the day and typically wake up around midday, where experienced sleepiness is lower than in the morning due to circadian rhythms (23). This may explain why the participants experience less difficulty awakening after night shifts compared with day work or days off despite having shorter sleep duration and not feeling refreshed.
Strengths and limitations
The study comprised a relatively large number of participants compared with previous field studies. In combination with the quasi-experimental (rather than observational) cross-over design and taking within subject variation into account in the statistical analyses, this is a strength of the study. We thereby enhanced internal validity by circumventing potential confounding from, eg, age and lifestyle factors, and accordingly we did not include these variables in the statistical analyses. The study was performed among experienced shift workers in a real-life setting, which enhances the external validity of the results. To avoid the risk of false positive findings due to multiple statistical testing, we considered $P<0.001$ to indicate statistical significance.
Another strength was the handling of the general limitations with cross-over designs, ie, possible order effects and carry-over between the different work schedules in the study. The order effect was limited by instructing the schedule planner to mix the different work schedules so they occurred in different orders, which resulted in 28%, 27%, and 45% of participants starting with 2+2, 4+4, or 7+7 work schedules, respectively. Carry-over effects were minimized by having a seven-day wash-out period without night shift work before the first night shift in a series. For practical reasons and in order to resemble real-life scheduling, recovery days were allowed to include both days off and day shifts. The rationale was that both are day-time oriented as opposed to days with night shifts and because this is the standard way to schedule night shift work among the police in Denmark. Since the normal day shift for police officers begin at 07:00 hours, it may be argued that police officers need to get up before their natural wake up time of days with day shift and that differences in the proportion of day shifts and days off would therefore bias the results. However, the bias is expected to be limited as there was a fair distribution of day shifts across the different work schedules (particularly 4+4 and 7+7) and awakening time on day shifts and days off differed by only 37

minutes.

Each work schedule was only performed once. As a consequence, it was only possible to study acute effects and not effects of long-term scheduling. However, effects of night shift work on sleep are generally acute and reversible, and we expect that the main potential differences between the three different work schedules in relation to sleep are covered with the present design. The study population consisted of male shift workers. Accordingly, we cannot be sure if the results extend to women, although similar biological mechanisms are likely. It may be speculated that permanent night work allows for better adaptation to daytime sleep because permanent night workers do not have to change their diurnal rhythms between night shifts (ie, on their days off). However, even permanent night workers are likely to being awake during the days on days off, eg, to be with family and for social reasons. Indeed, it has been shown that only a very small minority (0.3%) of permanent night workers show "complete" adjustment of their endogenous melatonin rhythm to night work (24). Yet, future research should address sleep and diurnal rhythms among workers with permanent night work.

In conclusion, we found that sleep duration was reduced after night shift work and did not increase with more consecutive night shifts. This leads to accumulated sleep debt with more consecutive night shifts. Furthermore, sleep duration was shortest and sleep quality particularly poor after the last night shift in a series of night shifts.

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Conflict of interest

The authors declare no conflicts of interest.

Sidebar

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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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Work-related exposure to violence or threats and risk of mental disorders and symptoms: a systematic review and meta-analysis

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ABSTRACT (ENGLISH)

Objective This review aimed to examine systematically the epidemiological evidence linking work-related exposure to violence and threats thereof with risk of mental disorders and mental ill-health symptoms. Methods We searched PubMed, EMBASE, PsycINFO and Web of Science to identify original studies that provide quantitative risk estimates. The evidence was weighted according to completeness of reporting, potential common method bias, and bias due to differential selection and drop out, selective reporting, and misclassification of exposure and outcome. Results We identified 14 cross-sectional and 10 cohort studies with eligible risk estimates, of which 4 examined depressive disorder and reported an elevated risk among the exposed [pooled relative risk (RR) 1.42, 95% confidence interval (CI) 1.31-1.54, I^2=0%]. The occurrence of depressive and anxiety symptoms, burnout and psychological distress was examined in 17 studies (pooled RR 2.33, 95% CI 3.17, I^2=42%), and 3 studies examined risk of sleep disturbance (pooled RR 1.22, 95% CI 1.09-1.37, I^2=0%). In most studies, common method bias and confounding could not be ruled out with confidence and strong heterogeneity in most outcome definitions invalidate the strict interpretation of most pooled risk estimates. Conclusion The reviewed studies consistently indicate associations between workplace violence and mental health problems. However, due to methodological limitations the causal associations (if any) may be stronger or weaker than the ones reported in this study. Prospective studies with independent and validated reporting of exposure and outcome and repeated follow-up with relevant intervals are highly warranted.

FULL TEXT

Headnote

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Conclusion The reviewed studies consistently indicate associations between workplace violence and mental health problems. However, due to methodological limitations the causal associations (if any) may be stronger or weaker than the ones reported in this study. Prospective studies with independent and validated reporting of exposure and outcome and repeated follow-up with relevant intervals are highly warranted.

Key terms anxiety; burnout; depression; psychological distress; sleep disturbance; workplace violence.

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Within the context of work, violence and threats thereof has been recognized as a widespread challenge in numerous studies. Estimates of the frequency vary considerable in the literature according to occupational setting, definitions, and measurement methods (1). In a 2018 Danish survey among 39 000 randomly selected employees aged 18-64 years, 5.8% reported exposure to physical workplace violence and 8.4% reported threats of violence at their workplace during the last 12 months (arbejdsmiljodata.nfa.dk). Workplace violence and threats thereof are reported to be highly prevalent in the healthcare sector and among social workers, teachers, police and prison personnel (2-14).

Though violence in the context of work is a recognized problem the definition of workplace violence is unclear. The International Labor Organization provides a broad definition of workplace violence as "Any action, incident or behavior that departures from reasonable conduct in which a person is assaulted, threatened, harmed, injured in the course of, or as a direct result of, his or her work". Thus violence can be either physical (such as attacks and beating) or psychological (such as threats and harassment). Since workplace violence is a widespread challenge, it is important to gain knowledge about its possible adverse consequences on mental health. At least three reviews have indicated that violence and threats thereof at the workplace are associated with increased risk of mental ill health (1, 15, 16). However, as reviews were descriptive and narrative in design, they neither provided meta-analyses nor systematically assessed risk of bias or grading of the strength of the evidence.

The hypothesis that workplace violence causes mental disorders is supported by the evidence that exposure to very severe psychological trauma of a catastrophic nature may result in severe psychological disorders, ie, posttraumatic stress syndrome (PTSD) during the following months (15). Although work-related violence and threats may be of catastrophic nature they are most often less severe. On the other hand, work-related violence is often prolonged or repeated, which may contribute to increased risk of mental disorders (16).

Thus, the objective of this article is to review systematically, meta-analyze and critically evaluate the epidemiological evidence for causal relations between violence or threats thereof at work and the risk of depressive and anxiety disorders (primary outcomes) and mental ill-health symptoms (secondary outcomes), respectively. In this review, work-related violence and threats thereof were defined as direct physical assault and/or threats of physical assault

taking place in the work context. Verbal aggressive or hostile communication/behavior and bullying/harassment that do not include physical assault or threats about physical assault were not included.

Methods

A review protocol was registered at PROSPERO (Prospero.org, number CRD42018087076) and the review was conducted and reported according to the PRISMA 2009 guidelines (supplementary data, www.sjweh.fi/show_abstract.php?abstract_id=3877, appendix A).

Search strategy and selection criteria

We searched the databases PubMed, EMBASE, PsycINFO and Web of Science (supplementary data, appendix B) and supplemented this by sifting through reference lists in retrieved papers and reviews.

We aimed to identify journal articles providing quantitative risk estimates for mental disorders and caseness of mental health symptoms in relation to physical violence or threats thereof at the workplace with the following inclusion criteria: (i) Fulltext papers in English in journals with peer-review published from the start of the current database up to 1 May 2018; (ii) Exposures: violence at the workplace defined as being exposed to direct aggressive physical assault or to threats of physical violence (oral or written intimidating or threatening statements, threatening behavior such as a raised fist, advancing behavior and stalking). Verbal assault and hostile behavior, bullying and sexual harassment were not included unless they explicitly involved physical violence or threats thereof; (iii) Primary outcomes: mental health disorders (depressive disorder (ICD10 F32-33) and anxiety disorder (ICD10 F40-41), but not PTSD and adjustment disorders (ICD10 F43) since these disorders are defined by their cause and are, therefore, not eligible in controlled observational studies of exposure-outcome relations in which the outcome must be defined independent of the exposure; (iv) Secondary outcomes: depressive symptoms, anxiety symptoms, psychological distress, burnout, comprising symptoms such as being physically or emotionally exhausted and feeling tired including emotional exhaustion and fatigue, and disturbed sleep and; (v) Exposure taking place within one year before execution of the study in order to exclude studies with a long or poorly defined time span between exposure and outcome (17). Only one study addressing life-time exposure to violence was excluded as a result of this criterion (18); (vi) Effect measures: indicators of relative or absolute risk of disorders or symptom caseness. Seven (19-25) cross-sectional or longitudinal studies addressing a diversity of symptom outcomes reporting correlation or regression coefficients based upon continuous exposure and/or outcome scores were not included since these studies were not eligible for meta-analyses based upon relative risk measures. Eight other studies were excluded because they did not provide any measure of association at all (8, 26-32).

Data extraction

Descriptive information and risk estimates were retrieved from each publication using a standardized form (table 1 and supplementary data, appendix C, tables S1-7). If physical violence was not distinguished from threats of violence, we categorized the outcome as the latter. If the relevant relative risks (RR) were not reported but data were available, we computed risk estimates and confidence intervals (CI) (five studies (33-37).

Quality assessment

Two authors independently reviewed the papers and considered the quality of each study using the instruments listed below. Discrepancies were resolved by consensus or involvement of a third author.

Completeness of reporting. Each publication was evaluated for completeness of reporting by considering the following study characteristics modified after Bonzini et al (38): study design, definition of study population, recruitment procedure, response rate, exposure ascertainment, outcome ascertainment, data analyses and statistical modelling.

We evaluated whether each of these study characteristics were described (score=1) or not (score=0). Giving equal weight to each of the eight items, we considered completeness of reporting as sufficient if the sum of the 0/1 scores for each paper was >6 (38). Completeness of reporting is not a direct measure of scientific quality or validity, but a measure of reporting quality.

Bias and confounding. We identified a priori the following potential types of bias of particular importance in the field: (i) Selection bias due to differential participation in cross-sectional and case-control studies or differential drop-out in

cohort studies with a risk of overrepresentation of exposed with disease. This may cause bias in either direction; (ii) Common method bias resulting from self-report of both exposure and outcome. This applies in particular to cross-sectional and case-control studies but may also affect cohort studies and is expected to inflate risk estimates; (iii) Non-differential misclassification between exposure and outcome resulting from crude or inaccurate methods of ascertainment. This is expected to deflate risk estimates; (iv) Selective reporting of results in studies with multiple analyses, which is expected to inflate risk estimates.

Confounding was considered unresolved unless sex, age, and socioeconomic status (measured with education, income or occupational class) were accounted for by analysis or design. For each type of bias, the risk was rated as high (score=1) or low (score=0), and we categorized a study at higher risk of bias when the sum of scores was >2.

Meta-analysis

In studies where exposure was divided into levels by severity or frequency and risk estimates were reported according to these levels, the highest level versus the reference category was selected for the meta-analysis. We computed a summary risk estimate across all stud- ies grouped by exposure and by primary and secondary outcomes. If a true risk exists, it is likely to differ across studies. Therefore random effects models were used for weighting odds ratios or equivalent [RR or hazard ratios] by the inverse variance. Heterogeneity was assessed by the I2 statistic. Meta-analyses were carried out in R version 3.4.4 using packages meta, metaphor and forest plot.

In supplementary analyses, we excluded studies with potential bias or missing information on two or more of the eight study characteristics that we evaluated. Potential publication bias was visualized by funnel plots displaying risk estimate variance by risk estimate.

Results

We identified 24 independent studies that fulfilled the eligibility criteria (figure 1): 10 cohort or nested case-control studies and 14 cross-sectional studies. Characteristics of the studies stratified by outcome are provided in table 1 (primary outcomes) and the online supplementary data, appendix C, tables S1-6 (secondary outcomes).

Information on exposure to workplace violence or threats thereof was retrieved by self-reports in questionnaires in 16 studies (33-37, 40-42, 44, 45, 47, 49, 50, 53-55), interviews in 6 studies (43, 46, 48, 51, 56, 57), a job exposure matrix (2), and records of compensation claims (39). Questions were most often 1- or 2-item questions such as "Have you been exposed to physical violence at your workplace during the last 12 months?" without further specification. These studies reported a prevalence of threats of violence of 0.8-20% and for violence a prevalence of 0.7-42%.

Two studies (40, 41) specified a list of 13-18 items of different forms of violent incidents and threats (prevalence of threats 18% and violence 23%), and eight studies (33-35, 42-46) applied multi-item scales developed in earlier research such as the Violent Incidence Form (VIF) with reported prevalences of threats of violence and violence of 12-27.7% and 9.2-75%, respectively (33, 42, 43), the Experience of Assault Questionnaire (prevalence of violence of 63.4%) (34) and the Workplace Violence in the Health Sector Country Case Studies Research Instruments reporting a prevalence of threats of violence of 24.2% and of violence from 5-15.6% (35, 44-46). One study used a job exposure matrix to assess the exposure to threats of violence and violence with a prevalence of 5.1-6.9% and 1.1-3.3%, respectively (2).

For outcome occurrence, prevalence also varied substantially across studies. The range of prevalence of depression in the reference group was 4-14%, (see table 1). Prevalence of depressive and anxiety symptoms in the reference group ranged 15-57% and 13-26%, respectively. For burnout, prevalence ranged 3-64%, for psychological distress 17-39%, and for sleep problems 5-30% (supplementary data, appendix C, tables S1-6). Completeness of reporting was satisfactory in most studies, but incomplete in seven, mostly due to a lack of information on data analyses and recruitment procedures.

The 24 studies provided a total of 41 risk estimates (none with absolute measures of risk) on the association between violence/threats of violence and mental health outcomes of which 39 were above unity. The overall summary RR was 1.70 (95% CI 1.47-1.95). Since the difference in the summary risk of exposure to violence (RR 1.47, 95% CI 1.28-1.68) and exposure to threats of violence (RR 1.82, 95% CI 1.43-2.31) was minor, the results are

presented together in the following.

Primary outcomes (psychiatric disorders)

Figure 2 depicts the four studies that addressed risk of depressive disorder (2, 39, 47, 48). The weighted averaged RR according to these studies was 1.42 (95% CI 1.31-1.54, I2=0%), Only one, a registry-based study, explicitly addressed risk of medically diagnosed depressive disorder (and other mood disorders), while two cohort studies used prescription of anti-depressive medication as a proxy measure of depressive disorder (39, 47). The last study used the revised version of the 20 item CES-D, possibly providing more reliable data on depressive disorder as evidenced by a prevalence of 6.6% in the reference group (48).

Secondary outcomes (mental ill-health symptoms and sleep problems)

Figure 2 also shows the estimates for depressive symptoms that were addressed in eight studies (ten risk estimates) (33, 34, 37, 45, 46, 49-51), including one cohort study. All studies reported a RR above unity (pooled RR 2.33 (95% CI 1.71-3.17, I2=42%)). The prevalence of depressive symptoms in the reference group was 15-57% and is therefore unlikely to indicate major depression (supplementary data, appendix C, table S1). Completeness of reporting score varied between four and eight and all studies were vulnerable to at least one type of bias (supplementary data, appendix C, table S7).

Figure 3 depicts estimates for anxiety, anxiety symptoms, psychological distress, burnout and sleep problems. Anxiety, assessed by prescribed anxiolytics was examined in one study that did not find an association with exposure to violence (47). Anxiety symptoms were reported in three studies (33, 50, 51) with a summary RR of 2.40 (95% CI 0.78-7.36, I2=90%). Completeness of reporting score ranged from five to eight and all studies exhibited two or three types of potential bias that we rated as important prior to our study (supplementary data, appendix C, table S7).

Burnout, including emotional exhaustion and fatigue, was examined in six studies (supplementary data, appen- dix C, table S5) (41, 43, 44, 52-54): three cohort studies and three cross-sectional studies. The summary estimate across all six studies was 1.60 (95% CI 1.25-2.05, I2=57%), figure 3. Completeness of reporting score ranged from six to eight. In all studies we assessed potential bias (supplementary data, appendix C, table S7).

Psychological distress was measured in four studies (35, 40, 42, 44) (six risk estimates) with four risk estimates above unity (supplementary data, appendix C, table S4). The summary estimate across all studies was 1.29 (95% CI 1.01-1.64, I2=58%), figure 3. Completeness of reporting score ranged from five to seven. In all studies, we assessed likely bias (supplementary data, appendix C, table S7).

Sleep problems were addressed in two cohort studies (36, 55) and one cross-sectional study (56) (four risk estimates). The summary risk estimate across all studies was 1.49 (95% CI 1.14-1.96, I2=0%) and the corresponding risk estimate for the two cohort studies were 1.22 (95% CI 1.09-1.37, I2 = 0%). Completeness of reporting score seven or eight. Risk of bias was considered unlikely in only one study (supplementary data, appendix C, table S7).

Exposure-response

Seven studies examined the exposure-response relation according to level or frequency of violent acts and five of these studies found the risk to be increased in parallel with increasing frequency of exposure (2, 43, 46, 54, 57), including one of the studies on depressive disorder (2). In two studies, the findings were inconsistent (36, 40).

Study design

Considering both violence and threats thereof and all outcomes together, the pooled estimates for the 10 cohort and case-control studies (RR 1.36, 95% CI 1.17-1.58) tended to be lower than the pooled estimates for the 14 cross-sectional studies (RR 1.92, 95% CI 1.55-2.37).

Publication bias

A funnel plot demonstrating the relationship between precision and magnitude of the risk estimate provides no strong indication that larger or more precise studies systematically report risks of smaller magnitude than small studies (figure 4). Thus, publication bias is unlikely.

Discussion

In this systematic review of the epidemiological evidence on the relation between workplace-related violence and threats thereof and mental health problems, we included 14 cross-sectional and 10 cohort studies.
The criteria for exclusion (verbal assault and hostile behavior, bullying, sexual assault and harassment) can be difficult to distinguish from the criteria for inclusion (threats of violence). The data on exposure depends on the perception, appraisal, and the state of the victim of the verbal assault, hostile behaviors or threats, making this an issue for comparability of studies. Threats were defined as verbal threats of directly physical violence or threats such as raised fits and advancing behavior. The strict definition of threats of violence applied in this review has reduced the number of eligible studies, but not necessarily the number of high-quality studies and studies addressing medical mental health outcomes and, therefore, may have few - if any - implications for the conclusions at which we arrive.
Exposure to violence is easier to define and distinguish from the other mentioned behaviors though sexual harassment (which we excluded in this review) in some situations can be perceived as violence.
Physical violence (bodily attacks) may be assumed in general to represent more severe exposure than threats of violence, and the pooled risk estimates we found for threats of violence and violence respectively also showed this tendency. However, the difference was small and the CI overlapped. Therefore, we argue that the most parsimonious approach is to study violence and threats thereof together.
The validity of the instruments used to measure exposure is another issue of concern. Half of the studies (12 studies) used 1-3 single questions, which may cause differential misclassification. However, the prevalences of violence/threats found in these studies (0.7-42%) are not much different compared to those found with the more validated measurement instruments (5-75%). The study using a job exposure matrix reported prevalence of threats of violence of 5.1-6.9% and 1.1-3.3% for violence, which are a bit lower than those found by the selfreported data. Since no systematic difference is observed across the measurements methods, analyses stratified by type of instrument is hardly informative. However, the very broad range of exposure prevalence across all the included studies reflects the strong heterogeneity, problems related to comparability, and emphasizes the lack of a uniform definition of workplace violence.
Fifteen excluded studies were not informative with respect to the primary outcome of this review (mental health disorders) because no risk estimates were provided. Although seven of these studies did provide alternative measures of association, they were not eligible for meta-analyses based on RR estimates of caseness and were therefore not considered further.
Consistency of risk estimates across studies with different designs, settings, and geographical regions was remarkable with almost all studies reporting an elevated risk in relation to work-related violence and threats thereof. In relation to the triangulation theory (58), this consistency across different study designs and populations supports a causal association. However, this consistency needs to be viewed in the light of the high variation in baseline outcome prevalence in the reference groups, which for instance for depressive symptoms ranged from 15-57%. Most likely this variation is due to differences in outcome definition and ascertainment rather than being a reflection of large variation of the occurrence of outcomes. None of the studies explicitly ascertained the depressive disorder diagnosis by a psychiatric interview, which is regarded as the most reliable method (59, 60). Moreover, the variety in the methods for assessment of violence and the quality of these measurements make it difficult to find clear causal relations.
Bias causing inflation of the risk estimates.
Information on exposure as well as outcome was obtained by questionnaire or interview in 20 of the 24 studies and are therefore not mutually independent observations. Since reduced psychological well-being or even a predisposition for mood disorders may influence perception and reporting of violence or threats, there is a risk for so-called common method bias, which is expected to inflate risk estimates (61-63) although the opposite may also be true (66). It might be speculated that reporting of threats is more prone to bias than reporting of violence which is more easy to prove - at least when it comes to severe cases of physical assault. However, the summary risk estimates of the two categories of exposure do not strongly deviate. We also assessed biased results due to selective reporting. Since we retrieved risk estimates by predefined criteria without considering the objectives of the

included papers, bias due to selective reporting is unlikely.

Bias causing deflation of the risk estimates

Selective inclusion where individuals who are healthy at baseline may represent a more robust survivor population - either because employees with mental health problems avoid jobs with a high potential for violence or because employees who became victim to violence and subsequently encountered mental health problems may have left the job before entering the study. In addition, some people would never consider working in a psychiatric ward or a prison, so self-selection into job might also play a role. Moreover, if violence is triggering a disorder without delay - as would be expected - and victims recover within some months, it may be difficult to detect an increased risk in follow-up studies with a long time-span from baseline reporting of violence and ascertainment of the outcome at follow-up. This could be the case for the cohort studies included in this review where follow-up intervals in most studies were two years. As shown, the summary estimates in the cohort and case-control studies tended to be lower than for the cross-sectional studies.

Another source of bias that likely results in attenuated risk estimates is misclassification of exposure in studies using job exposure matrices, but this only applied to one study in this review.

Confounding

We evaluated confounding by sex, age, and socioeconomic status according to the a priori published protocol. In addition, mental health status may profoundly influence reporting of being subjected to violence or threats thereof, aggressive behaviors of clients or patients and risk of later mental disorders or distress. Evidence for an association of mental health status and risk of bullying was found in a prospective study showing that individuals reporting mental distress exhibited a higher risk of being bullied two years later (64), although another explanation for this result could also be that individuals exhibiting signs of mental distress were more often targeted by perpetrators of bullying. However, this may not be a major source of bias in cohort studies included in this review since baseline mental health was controlled for in all the cohort studies except two (41, 54).

Concluding remarks

The reviewed studies consistently indicated associations between workplace violence and mental health problems. However, due to the methodological limitations of most of the studies, bias and confounding could not be ruled out with confidence and causal associations between violence/threats of violence and mental disorders and mental health symptoms (if any) may be stronger or weaker than the pooled estimates from the meta-analyses. Prospective studies with independent and validated reporting of exposure and outcome and repeated follow-up with relevant intervals are highly warranted.

Acknowledgements

The Danish Working Environment Research Fund (reference number 52-2017-09) financed this project. An English-language report of the study has been submitted to the Danish Labor Market Insurance and is expected to be published on the Labor Market Insurance's homepage. The authors declare no conflicts of interest.

Sidebar

In this first systematic review of the epidemiological evidence on risk of mental health problems following workplace violence and threats of violence, we identified 24 studies that with few exceptions reported increased risk of depressive disorder and mental health symptoms. However, due to methodological limitations causal associations (if any) may be stronger or weaker than the ones reported in this study.

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Additional material

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Neurodevelopmental disorders among young adults and the risk of sickness absence and disability pension: a nationwide register linkage study

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ABSTRACT (ENGLISH)

Objectives Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and learning disabilities (LD) have an early onset and often persist into adulthood, although their relative contribution to incapacity for work is unclear. We examined this issue among young adults with ADHD, ASD or LD taking into account socioeconomic factors and comorbid mental disorders. Methods Recorded diagnoses between the ages of 10-35 years between 2001 and 2010 were derived from nationwide inpatient and specialized outpatient hospital registers in Sweden. We identified 15 632 individuals with a main diagnosis of ADHD, 8238 with ASD, and 1038 with LD, and the matched control group without recorded mental disorders (N=124 536). The outcome was the number of register-based sickness absence and work disability pension (SA-DP) days during a maximum of three years follow-up. Results Among men, the rate ratio (RR) of SA-DP was 11.17 [95% confidence interval (CI) 9.89-12.60] for ADHD, 35.59 (95% CI 30.30-41.81) for ASD, and 9.20 (95% CI 5.76-14.70) for LD, in comparison to those in the reference group. The corresponding risks among women were RR 12.05 (95% CI 10.30-14.09) for ADHD, RR 28.36 (95% CI 22.96-35.02) for ASD, and RR 9.60 (95% CI 5.83-15.81) for LD. The findings were, to a large extent, similar when individuals on DP at baseline were excluded. Comorbid mental disorders further increased the risk of SA-DP. Educational differences were smaller among the patients than in the reference group. Conclusions Early-onset neurodevelopmental disorders, particularly with comorbidity, have a far-reaching impact on adult life in terms of SA and DP.

FULL TEXT

Headnote

Objectives Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and learning disabilities (LD) have an early onset and often persist into adulthood, although their relative contribution to incapacity for work is unclear. We examined this issue among young adults with ADHD, ASD or LD taking into account socioeconomic factors and comorbid mental disorders.

Methods Recorded diagnoses between the ages of 10-35 years between 2001 and 2010 were derived from nationwide inpatient and specialized outpatient hospital registers in Sweden. We identified 15 632 individuals with a main diagnosis of ADHD, 8238 with ASD, and 1038 with LD, and the matched control group without recorded mental disorders (N=124 536). The outcome was the number of register-based sickness absence and work disability pension (SA-DP) days during a maximum of three years follow-up.

Results Among men, the rate ratio (RR) of SA-DP was 11.17 [95% confidence interval (CI) 9.89-12.60] for ADHD, 35.59 (95% CI 30.30-41.81) for ASD, and 9.20 (95% CI 5.76-14.70) for LD, in comparison to those in the reference group. The corresponding risks among women were RR 12.05 (95% CI 10.30-14.09) for ADHD, RR 28.36 (95% CI

22.96-35.02) for ASD, and RR 9.60 (95% CI 5.83-15.81) for LD. The findings were, to a large extent, similar when individuals on DP at baseline were excluded. Comorbid mental disorders further increased the risk of SA-DP. Educational differences were smaller among the patients than in the reference group.
Conclusions Early-onset neurodevelopmental disorders, particularly with comorbidity, have a far-reaching impact on adult life in terms of SA and DP.
Key terms ADHD; attention-deficit hyperactivity disorder; autism; learning disability; register study; sick leave.
Key terms: ADHD; attention-deficit hyperactivity disorder; autism; disability pension; learning disability; neurodevelopmental disorder; register study; sick leave; sickness absence; young adult
Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and learning disabilities (LD) usually begin in childhood and may significantly impact the future lives of affected children. These disorders often persist into adulthood, may increase the risk of other mental disorders, and are associated with failure in developmental tasks such as gaining education and employment (1-10). The prevalence of ADHD, ASD, and LD among adults has been estimated to be around 4% (11), 1% (12), and 1-2.5% (13), respectively, although exact estimates for adults are seldom available. Economic costs in terms of special educational needs, healthcare services, and productivity loss in the labor market are substantial (1, 10, 14-17). Comorbid diseases are believed to be major drivers of healthcare utilization and cost (15-17).
The effects of early-onset neuropsychiatric and behavioral disorders may be particularly detrimental during young adulthood, since this period includes important developmental tasks, such as completing an education and entering into the labor market. To date, most studies have focused on ADHD, with the outcome usually being general 'productivity loss' measured as costs (1, 17) or occupational injuries (18). Two studies reported increased sickness absence (SA) days, assessed by self-reported days during the past month (15, 19). More short-term disability days but no difference between the likelihood of SA among workers with and without ADHD was reported in one study (16). However, these three studies did not examine other disorders than ADHD (15, 16, 19) or relied on self-reported outcome data (15, 19). We are not aware of any studies that have compared ADHD, ASD, and LD or examined whether socioeconomic factors and comorbid conditions are associated with the incapacity for work outcomes in these disorders.
Using register data covering the whole population of Sweden, we examined the longitudinal associations of ADHD, ASD, and LD with SA and disability pension (DP) among young adults, in comparison to those in a matched reference group without recorded mental disorders, and assessed the contribution of socioeconomic characteristics and comorbid mental disorders.
Methods
Participants and procedure
The study population was a register-based cohort derived from the whole population's register in Sweden, linked to in- and specialized outpatient registers between 2001 and 2010 (figure 1). The Regional Ethical Review Board, Stockholm, Sweden, approved the project. Statistics Sweden's Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) was used to obtain information on sex, age, education, birth country, and type of living area. The National Board of Health and Welfare provided data from the patient register (diagnosis-specific data on inpatient hospitalizations and specialized outpatient care), coded according to the International Classification of Diseases (ICD-10) and date of death. The National Social Insurance Agency provided information on annual days of SA-DP (the MIDAS register).
In Sweden, all individuals aged >16 years are entitled to SA benefits if they have income from work or unemployment benefits and have work incapacity due to disease or injury. All people aged 19-64, including those with no previous income, can be granted DP if their work capacity is long-term or permanently reduced due to disease or injury. For people aged >30 years, work incapacity has to be permanent before DP can be granted. Between ages 19-29, work incapacity needs to last for at least one year and can be granted to those still in school.
The individuals with neurodevelopmental disorders were those who had been 10-35 years old when their ADHD (International Classification of Diseases, ICD10 code F90), ASD (F84.0, F84.1, F84.3, F84.5, F84.8, F84.9), or LD

(F81) was recorded as the main diagnosis in the specialized in- or outpatient healthcare between 2001-2010. An additional inclusion criterion was living in Sweden five years prior to the treatment episode of specialized healthcare. Of the 24 908 individuals with a recorded diagnosis of ADHD, ASD, or LD, 65% were aged 10-18 at the time of their diagnosis in specialized healthcare, whereas 35% were aged 19-35 years.

We randomly selected five matched reference individuals (N=124 536) to each ADHD, ASD, and LD patient and matched them according to age, sex, type of living area, and birth country. The reference group had no indication of mental disorder (ICD-10 code F00-F99) in any of the hospital records. The individuals in the reference group had been living in Sweden five years prior to the cohort entry date of the patient with whom they were matched. A maximum of three years followup of annual net days of SA-DP began from the date of diagnosis, except when age at diagnosis was <19 years, in which case the follow-up began at the age of 19 (the eligibility age for DP in Sweden). The mean follow-up was 2.63 [standard deviation (SD) 0.69] years. The duration of follow-up depended on the year of entry into the cohort, death, and emigration. A total of 2593 individuals died or emigrated from Sweden during follow-up.

Covariates included sex, age, educational level (low: 0-9, intermediate: 10-12, high: >13 years), birth country (Sweden, other), type of living area (large city, medium sized town, small town/village), and comorbid mental disorders before or at the time of the main diagnosis, also derived from inpatient and specialized outpatient registers. Comorbidity also included mental retardation (ICD-10 codes F70-F73, F78, F79) (20). We used the MIDAS work DP register to identify those who were on work DP at the beginning of follow-up.

Statistical analysis

Descriptive statistics (N, %) for each diagnostic group and the reference group were calculated for covariates. We calculated annual and 3-year net number of SA-DP days for each person (based on the sum of SA-DP). We applied negative binomial regression procedure to produce rate ratios (RR) and their 95% confidence intervals (CI) to estimate the difference in SA-DP between individuals with ADHD, ASD, or LD, and the reference group. The offset variable was logarithmically transformed duration of follow-up (maximum three years) calculated for all individuals. Models were adjusted for socioeconomic factors and the calendar year when follow-up began. The analyses were repeated among a sub-group of individuals who were not on DP at the beginning of follow-up. Further analyses were carried out separately among cases and the control group to examine the association between socioeconomic factors and SA-DP, and among cases, the association between comorbid mental disorders and SA-DP. We used SAS statistical software (9.4) (SAS Institute, Inc, Cary, NC, USA).

Results

Table 1 presents the descriptive characteristics of individuals with ADHD, ASD and LD, and the reference group without recorded mental disorder. The largest diagnostic group was ADHD (N=15 632), followed by ASD (N=8238), and LD (N=1038). Men and those with low education were overrepresented in all the diagnostic groups. The highest prevalence of comorbid mental disorders was found among individuals with ASD (48%) and the majority of individuals with ASD (63%) were on DP already at the beginning of follow-up. The corresponding proportions for ADHD and LD were 22% and 21%, respectively.

Multivariable-adjusted RR for SA-DP days during the 3-year follow-up among men and women are presented in table 2. Compared to the reference group, ASD was associated with a 35.6-fold risk of SA-DP among men and a 28.4-fold risk among women. ADHD was associated with an 11.2-fold risk among men and a 12.1-fold risk among women whereas LD was associated with 9.2-fold risk among men and 9.6-fold risk among women. The findings were largely similar among a sub-group consisting men and women not on DP at the beginning of follow-up although the absolute rates were remarkably lower.

Among the patient groups, comorbid mental disorders further increased the SA-DP risk (table 3). The greatest RR (1.76) associated with comorbidity was found among those with ADHD. In ASD, the RR was 1.14 and in LD, the RR was 1.62 although not statistically significant in the latter group. Rather similar results were found among a sub-group of those not on DP at the beginning of follow-up.

The associations between baseline socioeconomic characteristics and SA-DP are presented in table 4. In all groups,

women had higher risk than men. There was much greater differences between educational groups among the reference group without mental disorders (RR for low versus high education 18.40) than among the patients (RR 2.98). However, the estimate for low education in the reference group diluted to RR 4.02 when the individuals on DP at baseline were excluded from the analysis (the corresponding RR 2.10 among the patient group). Living in a small town or rural area was rather consistently associated with higher risk of SA-DP when compared to living in a big city. Non-Swedish birth country was associated with lower risk of disability among the reference group without mental disorders, while no differences were observed in the patient group.

Table 5 shows the annual difference between diagnostics groups and the reference group. Although the overall pattern was similar to the original analyses, the differences seemed to slightly increase among men and slightly decrease among women.

Discussion

In this register-based prospective study of the workingage population in Sweden, we found high risk in terms of SA-DP associated with ADHD, ASD and LD. Two in three of the patients were treated in the specialized healthcare during childhood or adolescence, which reflects the early onset of these disorders. Compared to the matched reference group without recorded mental disorders, ASD was associated with the greatest burden of SA-DP with a 36-fold risk among men and 28-fold risk among women. Of them, 63% were already on DP at the beginning of follow-up. The corresponding risks among men and women with ADHD were 11 and 12; and among men and women with LD, 9 and 10, respectively. However, comorbid mental disorders played a significant role, further increasing the SA-DP risk. Educational disparities in SA-DP were smaller in the patient than reference group.

Our findings suggest that ASD is associated with the greatest burden of SA-DP. ASD represent a category of disorders that are characterized by difficulties in social reciprocity, communication and unusual or repetitive behavior. Among high-functioning people with ASD, difficulties in communication and social interaction rather than their actual work performance have been suggested to be the greatest obstacles to employment (4). Incapacity for work reflects a mismatch between job demands and an individual's capacity to respond to these demands due to a physical disease or mental disorder. However, people with ASD often have special, although narrow skills and high competence, and it may be possible to support their employment and capacity for work. They may need specific support at the workplace; eg, specific time devoted to communication and a structured, non-complex work environment (4).

Our findings correspond with previous studies that have shown associations between ADHD and selfreported one-month SA days (15, 19), and short-term disability days (16). ADHD is associated with symptoms that may substantially reduce work performance, such as abnormal attention, impulsiveness, hyperactivity or restlessness, disorganization, and time management and memory problems (14). People with ADHD may also have problems in motor coordination as well as in working memory, planning and anticipation, verbal fluency, effort allocation, and self-regulation of emotional arousal. However, they often have a high level of energy and enthusiasm, which may be a great advantage in favorable circumstances. Therefore, it has been recommended that regarding employees with ADHD, special attention should be paid to calming the work environment (eg, by avoiding noise and open offices). They should be allowed to move during the workday and receive help in organizing and keeping time schedules, and planning work tasks. They should be able to delegate work and receive support from supervisors and co-workers (14). Early ADHD has been found to be associated with later mental and substance use disorders, early pregnancy, school drop-out and criminality (5), which provides an idea of the potential mechanism linking early ADHD with future incapacity for work. In addition, behavior-based treatments may be effective, in addition to stimulant medication treatment (21).

LD refers to a heterogeneous group of neurodevelopmental disorders that influence the individual's ability to maintain, process or convey information to others effectively (22). This is often comorbid with other neurodevelopmental disorders such as ADHD (2). The literature on adult outcomes of LD is limited, and focuses mainly on educational and employment outcomes, showing mixed findings. The authors of a recent systematic review (2) concluded that comorbid mental disorders are the primary drivers of unfavorable outcomes in LD and a

source of heterogeneity among previous studies. Our findings give some support to this hypothesis although the associations of comorbidity were not statistically significant.

Of the socioeconomic factors, educational disparities in SA-DP were smaller in the patient groups than the reference group without recorded mental disorders. It is possible that having a neurodevelopmental disorder per se is highly disabling and therefore less affected by social or environmental factors. There is some evidence from the US that neurodevelopmental disorders, such as ASD are underdiagnosed among socioeconomically disadvantaged groups due to worse resources and poorer access to health services compared to more affluent groups (23). If this was the case also in Sweden, proportionally more undiagnosed cases with socioeconomic disadvantage would have been in our reference group. These issues need to be investigated in detail in future studies. In general, the reference group consisted of young people who were not treated in specialized mental healthcare but may have had treatment contact in primary healthcare.

The specific strength of this study is its design based on nationwide registers that cover the entire Swedish population, and the high coverage and good validity of the Swedish health registers (24). The large database enabled us to investigate young adults with relatively rare neurodevelopmental disorders. The associations were quite similar in sub-group analyses excluding those with DP at baseline, although the absolute rates were lower, as expected.

However, the number of individuals with LD was lower than would be expected from prevalence statistics; the individuals with LD in our study were probably severe enough to be treated in a specialized healthcare setting. Furthermore, some individuals may have had their diagnosis before age 10 and not been in contact with specialized healthcare after that. However, as the registers cover both specialized outpatient clinics and inpatient healthcare, we do not consider this a major source of misclassification. Regarding comorbidity, some milder comorbid disorders, such as milder depressive disorders, may have had been misclassified because they are often treated in primary healthcare. The follow-up in our study was three years which reflects relatively short-term impacts of neuropsychiatric diseases in adult life. Work incapacity usually increases with age, thus future studies with longer follow-up may observe greater increases. The MIDAS register of SA-DP is valid in terms of high coverage and being based on a physician-assessed diagnosis of a disease and disability. One limitation is that our findings may be generalizable to cases treated in specialized healthcare and may not be generalizable to countries with very different social and healthcare systems. Finally, there are other risk and protective factors that were not assessed in the present study.

In conclusion, our findings suggest that ADHD, ASD, and LD have major effects on the lives of young adults in terms of incapacity for work. The greatest burden was found to be associated with ASD. Specific attention should be paid to co-occurring mental disorders that considerably impair the prognosis. Efforts to improve employment in these groups may include, for example, the individual placement and support (IPS) method which has been shown to be effective among young adults (25).

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The authors declare no conflicts of interest.

Sidebar

This register-based study of the entire Swedish population found that attention-deficit/hyperactivity disorder, autism spectrum disorder, and learning disabilities had major effects on the lives of young adults in terms of sickness absence and disability pension. For the first time, we also examined the contribution of socio-demographic factors and comorbid mental disorders to the examined outcomes.

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Effectiveness of adding a workplace intervention to an inpatient multimodal occupational rehabilitation program: A randomized clinical trial

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ABSTRACT (ENGLISH)

Objectives This study aimed to evaluate the effectiveness of a workplace intervention (WI) added to an inpatient multimodal occupational rehabilitation program (I-MORE) on sickness absence. Methods In this researcher-blinded randomized controlled trial with parallel groups, individuals on sick leave due to musculoskeletal, unspecified- or common mental health disorders were randomized to I-MORE (N=87) or I-MORE+WI (N=88). I-MORE lasted 2+1 weeks (with one week at home in between) and consisted of "acceptance and commitment therapy", physical exercise, and work-related problem solving. The additional WI consisted of a preparatory part, a workplace meeting involving the sick-listed worker, the employer, and the primary rehabilitation therapist at the rehabilitation center, and follow-up work related to the meeting. The primary outcomes were number of sickness absence days and time until sustainable return to work (RTW) during 12 months of follow-up, measured by registry data. Results The median number of sickness absence days during the 12-month follow-up for I-MORE was 115 days [interquartile range (IQR) 53-183] versus 130 days (IQR 81-212) for I-MORE+WI. The difference between groups was not statistically significant (P=0.084). The hazard ratio for sustainable RTW was 0.74 (95% confidence interval 0.48-1.16; P=0.192) in favor of I-MORE. Conclusions This study provided no evidence in favor of I-MORE+WI compared to only I-MORE for long-term sickness absent individuals with musculoskeletal-, common mental- or unspecified disorders.

FULL TEXT

Headnote

Objectives This study aimed to evaluate the effectiveness of a workplace intervention (WI) added to an inpatient multimodal occupational rehabilitation program (I-MORE) on sickness absence.

Methods In this researcher-blinded randomized controlled trial with parallel groups, individuals on sick leave due to musculoskeletal, unspecified- or common mental health disorders were randomized to I-MORE (N=87) or I-MORE+WI (N=88). I-MORE lasted 2+1 weeks (with one week at home in between) and consisted of "acceptance and commitment therapy", physical exercise, and work-related problem solving. The additional WI consisted of a preparatory part, a workplace meeting involving the sick-listed worker, the employer, and the primary rehabilitation therapist at the rehabilitation center, and follow-up work related to the meeting. The primary outcomes were number of sickness absence days and time until sustainable return to work (RTW) during 12 months of follow-up, measured by registry data.

Results The median number of sickness absence days during the 12-month follow-up for I-MORE was 115 days [interquartile range (IQR) 53-183] versus 130 days (IQR 81-212) for I-MORE+WI. The difference between groups was not statistically significant (P=0.084). The hazard ratio for sustainable RTW was 0.74 (95% confidence interval 0.48-1.16; P=0.192) in favor of I-MORE.

Conclusions This study provided no evidence in favor of I-MORE+WI compared to only I-MORE for long-term sickness absent individuals with musculoskeletal-, common mental- or unspecified disorders.

Key terms RCT; return to work; RTW; sickness absence; sick leave.

Key terms: effectiveness; occupational rehabilitation program; randomized clinical trial; RCT; return to work; RTW; sick leave; sickness absence; workplace intervention

Sickness absence is a vast challenge in the western world, with consequences both for the sick-listed worker and society (1-3). Thus, several return-to-work (RTW) interventions have been assessed in the past decades with inconsistent results (4-9). However, studies suggest that multimodal interventions (10) could be important, particularly when adding workplace interventions (WI) (10-13). Most of these studies have recruited sick-listed workers with musculoskeletal complaints and low-back pain. Although studies also suggest that WI could be promising for individuals with common mental health disorders (6), the results are inconsistent (13).

In Norway, 3-4 weeks of inpatient multimodal occupational rehabilitation (I-MORE) is common for long-term sick-listed individuals with complex biopsychosocial barriers for RTW. Such programs are usually transdiagnostic, consisting of physical exercise, cognitive behavioral therapy, patient education, and work related problem solving

(14-16). In a recent randomized clinical trial, we found that a 3.5-week I-MORE reduced sickness absence compared with an outpatient cognitive behavioral intervention (unpublished data) (17, 18). Still, very few of the participants had been in contact with the workplace or their employer during the rehabilitation program (19). Thus, we adjusted the 3.5-week program to include a WI. This randomized clinical trial compared I-MORE to I-MORE+WI. We hypothesized that adding WI to I-MORE would lead to faster sustainable RTW and less sickness absence days.

Methods

This researcher-blinded randomized clinical trial (RCT) comparing parallel groups is described in detail in the protocol article (20). The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study (No:2014/2279), which was registered at clinicaltrials.gov (NCT02541890). The results are presented according to the CONSORT statement (21).

Participants

Individuals living in Trøndelag county in Central Norway were eligible to participate if they: (i) were aged 18-60 years, (ii) were sick listed 2-12 months, (iii) were employed in at least a 20% position (eg, >1 day per week), (iv) had an employer, (v) had a sick leave status of >50% off work, (vi) anticipated >4 more weeks of sick-leave, and (vii) had a diagnosis within the musculoskeletal, psychological or general and unspecified chapters of International Classification Primary Care, version 2 (ICPC-2). Potential participants were recruited in one of two ways: identified in registers from the Norwegian Labor and Welfare Administration (NAV) and invited through a letter or referred from their general practitioner. At the outpatient screening clinic, a physician, psychologist, and a physiotherapist assessed eligibility. Exclusion criteria were any of the following: being self-employed, having or being under consideration for a serious somatic or mental health/substance abuse disorder, currently undergoing rehabilitation, having significant problems with working in a group, insufficient comprehension of Norwegian language to participate in group sessions and to complete questionnaires, scheduled for surgery within the next six months, or being pregnant.

Interventions

I-MORE. The I-MORE program took place at Hysnes Rehabilitation Center, established as a part of St. Olavs Hospital in Trøndelag, Norway. The program lasted four weeks: two weeks at the rehabilitation center, one week at home, and one week at the center. The program consisted mainly of "acceptance and commitment therapy" (ACT; third generation cognitive behavioral therapy) (22), physical exercise training, and group- and individual sessions of work-related problem-solving resulting in a RTW plan. See table 1 for more information about the full content. An interdisciplinary team consisting of a psychologist, physiotherapist, exercise physiologist, nurse, physician and welfare caseworker provided the rehabilitation program. A certified ACT instructor supervised the coordinators monthly during the intervention. In addition to the multidisciplinary team, each participant was appointed a primary rehabilitation therapist as a contact person. The participants had several individual meetings with their primary rehabilitation therapist designing the RTW plan. The experiences from the week at home were used to try out new coping strategies and adjust the RTW plan. A more detailed description of the program has been published elsewhere (20).

I-MORE+WI. The workplace intervention consisted of (i) preparations before the workplace meeting, (ii) the workplace meeting, and (iii) writing a summary of the meeting (table 1). The preparations consisted of using a part of the scheduled meetings between the participant and their primary rehabilitation therapist to discuss the workplace meeting. In addition, there was a group meeting to talk about expectations, challenges and the value of RTW. The coordinator contacted the participant's employer before the meeting. They informed the employer about the agenda for the meeting, which included using a booklet called A Conversation about Work Possibilities. Developed by NAV, the booklet is a function assessment tool and often used for RTW problem solving (23). It contains questions about the individual's work and potential barriers for RTW and is a tool developed for professionals working with sicklisted individuals. The workplace meeting took place in week three (the week at home). The aim of the meeting was to discuss possibilities and progress for RTW. The meeting was scheduled for two hours and most commonly included the participant, the employer, and the primary rehabilitation therapist. The participant's general physician and/or

labor and welfare caseworker at NAV were informed about the meeting and was involved when appropriate. The rehabilitation therapist contacted the employer after the meeting to ensure that the plans and actions agreed upon in the meeting was followed up and completed. The participant and the rehabilitation therapist discussed the outcome and experiences from the meeting. A summary from the meeting, concluding what had been agreed upon, was written and sent to all participants. The summary was also added to the RTW plan and sent to the general practitioner and the NAV case worker.

Study context

In Norway, all legal residents are included in the public insurance system. Medically certified sick leave is compensated 100% the first 12 months. The employer pays for the first 16 days and the remainder is paid by NAV. It is encouraged to consider graded sick leave (20-100%), independent of employment fraction. After 12 months of sick leave, it is possible to apply for more long-term medical benefits: work assessments allowance and permanent disability benefits, both of which compensate approximately 66% of prior income.

Outcome measures

During 12 months of follow-up, register data was collected for sick leave payments, sick leave certificates, work assessment allowance and disability pension. The primary outcome measures were (i) cumulated number of sickness absence days during 12 months of followup after inclusion and (ii) time until sustainable RTW in the follow-up period, defined as four weeks without receiving medical benefits.

Randomization

Eligible individuals who passed the outpatient screening were randomized to I-MORE or I-MORE+WI. Block randomization with unknown sizes was performed by a web-based program delivered by a third party, the Unit for Applied Clinical Research at the Norwegian University of Science and Technology. It was not possible to blind the participants and the caregivers. Researchers were blinded until the analyses were completed.

Sample size

To analyze between-group differences with Kaplan Meier survival analysis with the log rank test with a hazard ratio (HR) of 0.6 (alpha 0.05, beta 0.20), would require 63 participants in each group. The use of register-based sickness absence data eliminates loss to follow-up in the intention to treat analysis of primary outcomes. To provide enough statistical power for questionnaire-based outcomes, the aim was 80 participants in each group (20). The sample size estimation was based on results in the field (24-26).

Statistical analysis

Sickness absence was registered both as number of days per month and as a dichotomous measure of whether or not the participant was registered on sick leave that month. We used monthly intervals (rather than exact dates) in order to contain all relevant sick leave benefits in the same measure, as exact dates were not available for payments and the long-term benefits. Number of days on sick leave was recalculated from a seven- to five-day work-week. Time on graded sick leave was recalculated to whole sick leave days. Sick leave days were adjusted for employment fraction and any increase in disability pension during follow-up was counted as sick leave.

Number of sickness absence days during 12 months follow-up after inclusion for the two groups were compared using the Mann-Whitney U (Wilcoxon rank sum) test, as sick leave days were not normally distributed. To analyze time to sustainable RTW, Kaplan Meier curves were estimated and compared with the log rank test. To estimate HR for RTW, we used the Cox proportional hazard model and the Efron method for ties (27). Time was calculated as the number of months until RTW, and participants were censored at full sustainable RTW or end of follow-up. Analyses were performed without adjustments and adjusted for age, gender, education, main diagnosis and length of sick leave at inclusion. The proportionality hazard assumption was checked using the Schoenfeld Residual test (28). The main analyses were performed in line with the intention-to-treat principle. In addition, we performed per protocol analyses excluding participants that withdrew after randomization (before or during the program) or did not want to do the workplace visit.

All analyses were done using STATA 14 (StataCorp, College Station, TX, USA).

Results

The flow of participants in the study is presented in figure 1. In total, 3086 potential participants were identified in the registers from NAV (between January 2015 and June 2016) and invited to take part in the study. Of these, 145 accepted the invitation and were invited for an outpatient screening at St Olavs Hospital. The number of patients referred from general practitioners to the outpatient screening was not available. After the outpatient screening, 175 participants were included in the study (111 from NAV registers and 64 referred from their general practitioner). All the workplace meetings in the WI were executed (100%), and lasted approximately two hours, as scheduled. Main themes in the meetings were the participants' health and work situation, the RTW process, perceived barriers during this process, as well as potential solutions.

Participants' characteristics

The participants were mainly women (79%) and the mean age was 46 (SD 9) years. About half had higher education (55%), and most worked full time (71%) prior to their sick leave, while 28% worked part time, and one individual had a graded disability pension. The median number of sickness absence days during the 12 months prior to inclusion was 184 days [interquartile range (IQR) 139-255]. A sick leave diagnosis within the musculoskeletal (44%) and psychological (43%) chapters of ICPC-2 were most common, while 13% were diagnosed with a general and unspecific diagnosis (chapter A). The baseline characteristics of the participants in the two programs were fairly similar (table 2).

Sickness absence

During 12 months of follow-up, the median number of sickness absence days for I-MORE+WI was 130 days (IQR 81-212), and 115 days (IQR 53-183) for I-MORE (figure 2). The difference between the groups was not statistically significant (Mann-Whitney U test, P=0.084).

In total, 46.8% (82 participants) achieved sustainable RTW during 12 months of follow-up; 37 participants (42%) in I-MORE+WI and 45 participants (52%) in I-MORE. The Kaplan Meier plot is shown in figure 3. The difference between the programs was not statistically significant (log rank test: P=0.190). The Cox regression analysis without adjustment gave a HR of 0.74 [95% confidence interval (CI) 0.48-1.16, P=0.192], in favor of I-MORE. The adjusted analysis showed similar results (HR 0.77, 95% CI 0.49-1.23, P=0.286). The per-protocol analysis did not provide any substantial changes in the estimates (results not shown).

Discussion

In contrast to our hypothesis, WI added to I-MORE did not facilitate work participation among adults on longterm sick leave with musculoskeletal, common mental or unspecified disorders. Rather, the estimates indicate that participants in I-MORE+WI versus I-MORE had an unfavorable impact from the WI, although there were no statistically significant differences between the programs.

Our results contrast with systematic reviews which conclude that WI in multimodal occupational rehabilitation increases RTW (10, 11). The results are also in contrast to comparable randomized clinical trials on WI and RTW (25, 26, 29, 30). Loisel et al (26) found that patients with low-back pain receiving a combined clinical and workplace intervention returned to regular work 2.4 times faster than those receiving usual care and that the workplace intervention accounted for most of the effect. The model was later replicated in the Netherlands where Anema et al (29) reported a RTW HR of 1.7 for the workplace intervention group compared to the control group. In another study, Bültmann et al (31) found 30% less sickness absence hours for an intervention including a workplace intervention compared to a more limited intervention. However, it should be noted that most of the aforementioned studies included participants with considerably shorter sick leave duration than our study (26, 29, 30); all were aimed at musculoskeletal disorders (25, 26, 29, 30) and none was conducted in an inpatient setting. However, despite including participants on long-term sick leave (median 150 days), Lambeek et al (25) found a substantial effect of integrated care for workers with chronic low-back pain (88 days versus 208 days until RTW) compared to the usual care group. Still, the intervention was quite extensive, in contrast to our study where the only difference between the groups was the WI.

Coordination between stakeholders is considered a key factor in helping sick-listed workers return to work (10, 11, 13, 32-35). In their systematic review, Carrol et al (11) concluded that involving the workplace alone is insufficient

and that coordination between stakeholders is necessary to increase RTW. The lack of coordination between stakeholders in the present study could therefore explain that there was no effect of the WI. Moreover, a previous study from our research group showed that I-MORE was effective in reducing sickness absence (unpublished data) (17, 18), the room for additional improvement from WI might be limited. Furthermore, the I-MORE program also included a work focus with work related problem solving and making of an RTWplan, which might have made the difference between the groups too small to add effect from the I-MORE. Even though there were no statistically significant differences between the programs, the estimates indicate more sickness absence days and a delayed RTW for I-MORE+WI. Although this should be interpreted with caution, it is possible that the WI somehow interfered with the RTW process.

The study was performed in a Norwegian context where the employer only pays for the 16 first days of sick leave, after which national insurance pays the remaining period of sick leave. Hence, there is not clear economic incentive for the employer to help the employee return to work. However, all the employers in this study agreed to participate in the workplace intervention, indicating a wish to take part in the employee's RTW process. Sickness absence is reimbursed 100% of the salary for the first 12 months in Norway. It could be argued that this takes away the incentive to return to work as fast as possible. However, the median sick leave before inclusion in the current study was 184 days, ie, during follow-up most participants would expend their sick leave period (maximum one year) and would then have to apply for more long-term benefits, which are only reimbursed 66%.

The main strength of this randomized study was the use of registry data for sickness absence measurements, ensuring no recall bias and no missing data. A limitation is the lack of information about the number of participants referred from general practitioners, as information was only available for the number of individuals that passed the outpatient screening. In addition, of the 3086 invitation letters that were sent out, only 145 (5%) accepted, limiting the generalizability of the results. Furthermore, potential participants had to be willing to do a workplace meeting, hence individuals with a problematic relationship with their employer or workplace, may have declined to participate in the study. In RCT, it is recommended to perform analyses adjusted for important predictors. A limitation in this study is the lack of information about participants' expectations at the start of the program. However, we performed sensitivity analyses adjusted for other important predictors such as education and length of sick leave at inclusion. Blinding of the participants or the healthcare providers at the rehabilitation center was not possible, however, the researchers were blinded, and two researchers performed the analyses separately.

Concluding remarks

When added to the I-MORE, the current WI did not facilitate work participation among individuals on longterm sick leave with musculoskeletal, common mental or unspecified disorders. Hence, this study provides no evidence in support of supplementing I-MORE with this limited WI for the current disorders. More research is needed on how the workplace can be effectively included in occupational rehabilitation.

Competing interest

The authors declare no conflicts of interest.

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Sidebar

This study provided no evidence in favor of adding a limited workplace intervention to an inpatient occupational rehabilitation program for long-term sickness absent individuals with musculoskeletal- or common mental. If anything, the estimates cautiously indicates an unfavorable impact from the current workplace intervention.

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DETAILS

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How leadership behaviors influence the effects of job predictability and perceived employability on employee mental health – a multilevel, prospective study

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ABSTRACT (ENGLISH)

Objectives This study aimed to elucidate the potential moderating effect of fair-, empowering-, and supportiveleadership behaviors on the relationship between job predictability, future employability, and subsequent clinically relevant mental distress. Method The study had a full panel, prospective design, utilizing online, self-administered questionnaire data collected at two time points, two years apart. Fair-, empowering-, and supportive-leadership behaviors, job predictability and future employability were measured by the General Nordic Questionnaire for Psychological and Social Factors at Work (QPS_{Nordic}). Mental health was measured using the 10-item Hopkins Symptom Checklist (HSCL-10), with cut-off set to >1.85 to identify clinically relevant cases. As data were nested within work units, a multilevel analytic approach was chosen. Results Individual-level direct effects: (i) higher levels of job predictability [odds ratio (OR) 0.83, 95% confidence interval (CI) 0.70-0.98], (ii) future employability (OR 0.83, 95% CI 0.74-0.93), (iii) fair- (OR 0.78, 95% CI 0.68-0.91), empowering- (OR 0.77, 95% CI 0.67-0.87), and supportive- (OR 0.71, 95% CI 0.61-0.81) leadership behavior, and (iv) the combination "quality of leadership" (OR 0.69, 95% CI 0.59-0.81) were significantly associated with a lower risk of reporting subsequent mental distress. Work-unit level direct effects: higher work-unit levels of fair- (OR 0.52, 95% CI 0.34-0.80) and empowering- (OR 0.61, 95% CI 0.40-0.94) leadership behaviors and quality of leadership (OR 0.54, 95% CI 0.34-0.87) were significantly associated with a lowered risk of subsequent mental distress. Cross-level interactions: No cross-level interaction effects were shown. Conclusions Leadership behaviors did not moderate the effects of job predictability and future employability on mental health. However, employees embedded within work-units characterized by fair, empowering and supportive leadership behaviors had a lower risk of subsequent mental distress.

FULL TEXT

Headnote

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Conclusions Leadership behaviors did not moderate the effects of job predictability and future employability on mental health. However, employees embedded within work-units characterized by fair, empowering and supportive leadership behaviors had a lower risk of subsequent mental distress.

Key terms direct effect; employee health; job insecurity; moderating; organizational change; psychosocial.

Key terms: direct effect; employability; employee health; job insecurity; job predictability; leadership; leadership behavior; mental health; moderating; multilevel; organizational change; perceived employability; prospective study; psychosocial

Contemporary work life is constantly changing, requiring both organizations and employees to adapt (1). Extensive workplace changes such as company restructuring and downsizing have been associated with adverse effects on employee health, work ability and productivity (2, 3). During change, employees' perceptions of job predictability and

future employability may be altered, possibly affecting mental health (4, 5). Mental illness is one of the stronger contributors to work disability worldwide (6). Common psychiatric disorders such as anxiety and depression are amongst the most prevalent (7) and associated with large societal and individual costs (8). Various types of organizational changes (2, 3) (the latter study was partly based on the same cohort as the present study) and psychosocial working conditions have been associated with symptoms of depression and anxiety (9, 10), in particular job security, ie, predictability regarding one's future job prospects (4, 11). As low job predictability affects an increasingly larger part of the working population (12), there is a pressing need to discern the impact on employee mental health. Moreover, in order to develop effective countermeasures, modifiable factors that may alleviate possible adverse impacts associated with low job predictability must be identified. The present study had two main aims: to (i) determine whether job predictability and future employability predicted employee mental health and (ii) assess the potential moderating effect of fair-, empowering-, and supportiveleadership behaviors at work-unit level on the effect of job predictability and future employability on employee mental health.

Employees experiencing organizational changes, such as restructuring or downsizing, have reported reduced predictability regarding current and future job prospects (4, 5, 13). Reduced predictability has also been shown to persist long after implemented change (14, 15) and is associated with health complaints, turnover, lowered productivity, job satisfaction, and low work engagement both in the short and long term (4, 11). Conversely, increased job predictability has been linked to trust in management, openness towards change, and lowered mental strain (16, 17). As the frequency and extent of organizational changes in contemporary work life are increasing, predictability regarding ongoing work arrangements as well as employability in the future has become a central concern for an increasing number of employees. Much of the change and job-related uncertainty present in contemporary work life may be inevitable, highlighting the significance of identifying factors that can be influenced in order to facilitate a healthy work life (18). However, less is known regarding potential modifiable moderators of the relationship between job predictability and health. If such factors can be pinpointed in the work environment, organizations may influence them through strategic interventions (19).

Leadership is one factor that is amenable to strategic interventions (20, 21). Leadership is defined as the ability and responsibility to guide others in achieving a goal through processes of formal and/or informal influence (22). Various leadership behaviors have been associated with health, coping, productivity, and performance (23, 24). The current study aimed to determine whether fair-, empowering-, or supportive-leadership behaviors moderated prospective effects of job predictability on employee mental health. Fair leadership is characterized by a strong focus on upholding procedural justice and ethics, transparency in decision-making and equal treatment (25). Empowering leaders maintain a strong focus on promoting employee participation, skill development, and enablement (25), while supportive leaders are attentive and considerate towards employees (26). Prior studies have indicated these dimensions to be separate, but related, aspects of leadership (27, 28). Leadership rated low in justice or support has been linked to health complaints, poor social climate, reduced productivity, and sick leave (29). Controversially, higher levels of justice and support have been associated with productivity, organizational commitment and citizenship behavior (30, 31). Acceptance of change and trust in management have also been reported in organizations where employees perceive justice to be prominent (26, 32).

Fair-, empowering-, and supportive-leadership behaviors may represent resources that may help employees cope with challenges associated with work related uncertainty. Support - both instrumental and emotional - and empowerment may help employees take an active role and promote appraisals of change and uncertainty as an opportunity rather than an unmanageable threat. Management operating according to pre-defined agreements may counteract fears of random and unjust treatment in uncertain situations. In addition to the individual perception of one's superior, the more general perception of leadership within a department or work unit may also influence the individual employee's sense of predictability and health. Working in environments generally characterized by high levels of these behaviors may prove protective as employees are immersed in a more generally positive work climate independently of their own specific work situation. Despite a widespread interest in the health impact of various aspects of the work environment, most studies of health effects of job predictability have considered only the

individual level. However, effects of job predictability on employee mental health may depend on both individual dispositions and characteristics of the context, eg, the working conditions within which employees are embedded. As employees within work units share superiors, leadership behavior in particular may constitute such a shared, contextual factor. Thus the present study utilized a multilevel analytical approach in order to take this potential shared group variance into account. In addition, aggregated, group-level predictors (eg, work-unit means) may reduce the influence of individual response characteristics, hence attenuating potential error due to response bias.

Hypotheses

Based on the above, three main hypotheses were tested. Figure 1 gives an overview of the hypothesized effects and directions.

Hypothesis 1: Individual-level direct effects. We hypothesized job predictability, future employability, and leadership behaviors to predict subsequent mental health.

Hypothesis 1.1: Higher levels of (i) job predictability and (ii) future employability at the individual level (ie, level 1) predicts a lower risk of reporting mental distress at follow-up, two years later.

Hypothesis 1.2: Higher levels of (i) fair- (ii) empowering-, and (iii) supportive-leadership behavior or (iv) "quality of leadership" (the combination of these three aspects) predicts a lower risk of reporting mental distress at follow-up.

Hypothesis 2: Work-unit level direct effect. The second hypothesis assessed the work-unit level, direct effect of job predictability, future employability and leadership behaviors on subsequent mental health - ie, the effects of work-unit levels of predictability, employability, and leadership behaviors on individual mental health.

Hypothesis 2.1: Employees embedded within work units characterized by higher levels of job predictability and future employability exhibit a lower risk of reporting subsequent mental distress.

Hypothesis 2.2: Work-unit employees characterized by higher levels of (i) fair-, (ii) empowering-, (iii) or supportive-leadership behaviors or the combination of these, (iv) "quality of leadership", exhibit a lower risk of reporting subsequent mental distress.

Hypothesis 3: Cross-level interaction effect. The third hypothesis assessed the potential cross-level interaction of leadership behaviors at work-unit level with job predictability and future employability in predicting subsequent mental health.

Hypothesis 3.1: Work-unit levels of fair- (i), empowering(ii), supportive-leadership behaviors (iii) or the combination of these, "quality of leadership" (iv), moderate the prospective relationship between the individual employee's job predictability or future employability and subsequent mental distress.

Method

Procedure and participants

The study was a part of the project "The New Workplace: Work, Health and Participation in Working Life", administered by the Norwegian National Institute of Occupational Health (STAMI). All data were collected by selfadministered online questionnaires, covering a wide range of demographic-, work- and health-related variables. The study had a full-panel, repeated-measures design. Baseline data were collected during 2009-2013, with followup after two years. A previous study investigated the effects of leadership and predictability on mental distress with data from the current project, with baseline data collected during 2004-2009 (10). To compare results, avoid overlapping samples, and possibly yield a sample more representative of contemporary working life, we selected subjects recruited for the baseline sample after 2009.

The participating organizations contacted STAMI with a general request for aid in a work environment survey or in response to an invitation to participate in the project published on STAMI's home page. All participating organizations were located in Norway and included a wide variety of professions in both the public and private sector. All current employees and managers in the participating companies were invited to take part in the study. In total, 8140 employees were invited at baseline. Of these, 5166 (63.6%) responded at baseline, while 3405 (65.7%) also participated at follow-up. Inclusion criteria was completing the outcome measure at baseline, while dropout was defined as not having completed the outcome measure at follow-up. For further details, see table 1.

Variables

Predictor: Job predictability and future employability. Job predictability and future employability were assessed by the General Nordic Questionnaire for Psychological and Social Factors at Work (QPSNordic) (25). Job predictability was measured by three items assessing to what degree employees know what tasks, co-workers, and superiors they can expect for the next month in their current job. Future employability was measured by the work factor "predictability of the next two years", with two items assessing the employee's confidence that they possess the competence and abilities needed to acquire an attractive job in two years. Responses on all items in both predictors were given on a 5-point Likert scale (range 1=very seldom to never to 5=very often or always). For both scales, a mean score was calculated. At baseline, Cronbach's a was 0.64 for job predictability and 0.73 for future employability. See the supplementary material for all included items (www.sjweh.fi/show_abstract.php?abstract_id=3880).

Predictor and moderator: Leadership behaviors. The three dimensions of leadership behaviors (fairness, empowerment and support) were assessed utilizing the QPSNordic (25). The mean of the three leadership factors was also calculated to reflect a more general scale of leadership, labelled "quality of leadership", as specified in the QPSNordic manual (25). Responses on all items were given on a 5-point Likert scale, ranging from 1=very seldom or never to 5=very often or always. At baseline, Cronbach's a was as follows fair leadership=0.86, empowering leadership=0.88, support from superior=0.85, and quality of leadership=0.90.

Outcome: Clinically relevant mental distress. The 10-item Hopkins Symptom Checklist (HSCL-10) (33) was employed to assess clinically relevant mental distress. HSCL-10 is a self-report instrument for assessing symptoms of mental distress (ie, symptoms of anxiety and depression) utilized in both clinical- and population studies (33, 34). For each item, a statement is presented and respondents are to report how the statement match their own experience within the last seven days. Responses are measured on a 4-point Likert scale ranging from 1=not at all to 4=very much. Cronbach's a at baseline was 0.86. Based on the ten items, a mean score was calculated. To identify clinically relevant cases, a cut-off was set to >1.85 and the reliability and validity of HSCL-10 have been demonstrated repeatedly (33, 34).

Potential confounders

Age, sex, skill level, and organizational change were included as potential confounders in all analyses. Age was arranged into four groups: (i) <29-39, (ii) >39-49, (iii) >49-59 and (iv) >59 years. Skill level categories were created using the International Standard Classification of Occupations (ISCO-88). The different categories reflect the number of years of formal education typically required to qualify for a certain profession: (i) <12, (ii) 13-15, and (iii) >15 years. Analyses were also adjusted for a number of distinct types of organizational changes as change may influence health by mechanisms not related to predictability.

Statistical analyses

Multilevel modelling. Multilevel logistic regressions (generalized linear mixed effects regression, GLMER) were employed to estimate the prospective associations due to the dichotomous outcome and the dataset nested structure. The organizations differed substantially in size and scope, ranging from one-unit organizations to organizations with several work units spread out over large geographical locations. As a result, we hypothesized employees within work units would share more contextual variables than employees within the total organization, and work-unit membership was designated as the grouping variable.

The multilevel approach takes into consideration the clustering of measurements. Not accounting for shared variance amongst measurements, eg, due to a shared environment, violates the assumption of independence, which may bias estimates, eg, underestimate standard errors (35) and increase the risk of type I error in the presence of a high within-group correlation of measurements, ie, high intra-class correlation (ICC) (36). As ICC indicate the degree to which measurements correlate within groups and variance is explained by between-group characteristics, ICC were estimated to assess the appropriateness of applying a multilevel approach. In the present sample, ICC were as follows: fair leadership=0.101, empowering leadership=0.071, and support from superior=0.082. An ICC of 0.05 indicates a small- to medium-sized group effect and has been suggested as a threshold for applying multilevel analyses (37). However, prior studies have selected ICC of 0.01 to indicate statistically significant group-level effects

in data (38). As the present ICC were in the range of 0.10-0.07, we considered it appropriate to apply a multilevel assessment.

Multilevel modelling provides the possibility to explore both individual- and work-unit level direct effects and cross-level interaction effects (35). To assess the associations at the individual- and work-unit level separately, ie, to separate the effects, the individual level predictor was group mean centered, while the predictor at work-unit level was the aggregated workunit mean (39). When group-mean centering scores at the individual level, the mean score of each employees' respective work unit is subtracted from each employee's individual score. The shared work-unit variance is then removed from the individual score, making the individual score uncorrelated with the work-unit mean. Thus, group-mean centering disentangles the effect of the predictor at the individual- and work-unit level and the effects can then be considered separately (39). In the multilevel model, variance parameters are estimated for both intercept and regression coefficient (slope) for all sample groups, in this case work units. For best model fit, both fixed and random effects may be incorporated to model variability. Fixed effects refer to effects equal for all groups, while random effects refer to effects that vary between groups. In a random intercept only model, the group intercept (intercept for each work-unit) is allowed to vary, while the regression coefficient (slope) is held constant for all groups. In a random intercept and slope model, both intercept and slope vary across groups (35). In the present analyses, both random intercept only and random intercept and random slope models were tested. For each model, likelihood ratio tests were used to ascertain best model fit. The random intercept only provided the best model fit for all models, except when including interaction terms, as the purpose was to estimate the effect of work unit levels of leadership behavior on variability of the slope at the individual level.

All analyses pertaining to direct and interaction effects were run in two steps: Model I was adjusted for the potential confounders age, sex, skill level and organizational changes, and model II was additionally adjusted for mental distress at baseline. Post-hoc analyses of the potential moderating effect of leadership behaviors at the individual-level were all adjusted for baseline mental distress. All analyses were run using IBM SPSS Statistics, version 25.0 (IBM Corp, Armonk, NY, USA) and R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set to $P<0.05$.

Results

Non-response and attrition analysis

Non-response was negatively associated with professions with unspecified/no formal requirements [odds ratio (OR) 0.61, 95% confidence interval (CI) 0.370.99]. Attrition analysis showed women were more likely to participate at follow-up (OR 1.31, 95% CI 1.18-1.46). Working in professions with >10 years of formal requirements (OR 4.33, 95% CI 1.95-9.63), 10-12 years (OR 1.20, 95% CI 1.05-1.37) and 13-15 years (OR 1.21, 95% CI 1.05-1.40) were also associated with participating at follow-up (table 2).

Hypothesis 1: individual-level direct effects

Predictability. Baseline adjusted analyses showed higher levels of job predictability and future employability at the individual level to be statistically significantly associated with lower risk of clinically relevant distress two years later, OR 0.84, 95% CI 0.71-0.99 and 0.82, 95% CI 0.73-0.93, respectively (table 3). For non-baseline adjusted analyses, see supplementary material, table S1.

1.2 Leadership. Baseline-adjusted analyses showed all included leadership behaviors at the individual level to be statistically significantly associated with a lower risk of reporting clinically relevant mental distress at followup: fair- (OR 0.81, 95% CI 0.69-0.94), empowering(OR 0.77, 95% CI 0.67-0.88), and supportive- (OR 0.71, 95% CI 0.62-0.82) leadership behavior and quality of leadership (OR 0.70, 95% CI 0.60-0.83). See table 3. For non-baseline adjusted analyses, see supplementary table S1.

Hypothesis 2: work-unit level direct effect

Predictability. Baseline adjusted analyses showed no statistically significantly prospective associations between work-unit levels of job predictability or future employability and mental distress. See table 4 for further details. For non-baseline adjusted analyses, see supplementary table S2.

Leadership. Baseline adjusted analyses showed higher levels of fair- and empowering leadership behaviors and

quality of leadership at work-unit level to be statistically significant associated with lower risk of reporting clinically relevant mental distress at follow-up. OR were as follows: fair- (OR 0.56, 95% CI 0.36-0.87), empowering(OR 0.64, 95% CI 0.41-1.00) leadereship behavior, and quality of leadership (OR 0.59, 95% CI 0.36-0.96). Work-unit levels of supportive leadership behaviors showed no statistically significant association with subsequent mental distress (table 4). For non-baseline adjusted analyses, see supplementary table S2.

Hypothesis 3: Cross-level interaction effects

Baseline adjusted analyses showed no statistically significant cross-level interaction effect of leadership behaviors at work-unit level (table 5). For non-baseline adjusted analyses, see supplementary table S3.

Discussion

The present results demonstrated higher predictability regarding one's present or future job prospects at the individual level to be associated with a lower risk of subsequent mental distress. These results are in line with prior studies linking higher levels of job predictability and future employability with positive effects on health (16) and low predictability to health complaints (11). Work-unit levels of job predictability and future employability were not associated with subsequent mental health, which indicate that generally high levels of unpredictability within work-units does not necessarily influence the mental health of individual employees. Thus, the health effects associated with work-related uncertainty seem less influenced by the general situation in one's respective work-unit, but rather depend on each employee's appraisal of their own situation.

The present results also showed higher levels of fair-, empowering- and supportive-leadership behaviors - and the combination of these, ie, "quality of leadership" - at the individual level were associated with a lower risk of reporting mental distress at follow-up. Work units characterized by higher levels of fair and empowering leadership behaviors and the combination of these were also found to have a protective, prospective effect on employee mental health. However, the effect of supportive leadership behaviors were no longer significant when measured at work-unit level. These results are in line with and adds to the findings of prior studies linking leadership characterized by fairness, empowerment and support to employee health (23, 24). Hence, results show that both individual and work-unit perception of leadership influence mental health prospectively. One notable exception was supportive leadership, which did not exhibit statistically significant associations at the work-unit level. Compared to fairness and empowerment, one may speculate that support from one's immediate superior constitutes more of a personal- and individual-level construct. Fair- and empowering-leadership behaviors consists of a range of aspects pertaining to the individual employee, but may also represent more general conducts defining organizational values and leadership expectations, which influence and applies to all member of a specific group or work-unit. Whereas support from one's superior may be mainly individual focused, representing a unique process and content for each individual employee depending on their needs and their superior's ability to meet these.

No significant cross-level interaction effect of leadership behaviors on the effect of job predictability and future employability on mental health was shown. These results contrast prior reporting leadership high in support and fairness to moderate the effect of workplace stressors on outcomes such as employee health, cooperation, and performance (40, 41). However, not all prior studies have shown such leadership dimensions to buffer the effect of stressors (42, 43). In sum, the included leadership behaviors did not moderate the effect of predictability on mental health; however, all leadership behaviors had a direct prospective, protective effect on subsequent mental health, at both the individual and work-unit level. Hence, management may focus efforts on promoting fair, empowering, and supportive superiors in order to promote employee health. Furthermore, one may speculate that the positive impact of leadership may partially stem from such leadership promoting a predictable and secure work environment. Hence, rather than leadership behaviors moderating the effects of low predictability, predictability may be one of the factors mediating the effects of leadership on mental health. A thorough investigation was outside the scope of the present study, however, post-hoc random intercept linear regressions were run to examine the effect of leadership behaviors on subsequent job predictability and employability. The results showed a statistically significant prospective effect of all leadership behaviors on both job predictability and future employability, providing preliminary support to this notion. For job predictability unstandardized betas were within the range of 0.02-0.04, for future employability betas

ranged from 0.05-0.09. For further details, see supplementary table S4.

It should be noted that cross-level interaction effects may be difficult to detect and could be affected by limitations of the present study, such as timeframe, level of measurement, lower statistical power due to fewer observations at work-unit level and variables not assessed in the analyses (39). Prior studies have found the level of analysis to influence the detection of the moderating effect of leadership on health, while others have found the moderating effect of supportive leadership only to be present in certain subgroups of the sample (44). On this note, in addition to being a group-level characteristic, leadership may also represent a unique relationship between supervisor and employee. The present results show leadership behaviors at the individual level have a direct effect on employee health, hence, leadership measured at the individual level could potentially capture different aspects of leadership, which group-level measures may not detect. In order to assess the potential moderating effect of leadership behaviors at the individual level, post-hoc individual-level interaction analyses were run. These did not show a significant moderation effect for any of the included leadership behaviors and were thus in line with the cross-level interaction analyses. For further details of the results of the individual level interaction analyses, see supplementary table S5. Although no difference in individual- or cross-lever interaction effects were shown in the present results, leadership represent both a shared and individual process, hence measuring the effect at both the individualand group-level may more accurately comprise the total effect of leadership, as shown in the significant direct effects at both the individual- and work-unit level.

Methodological considerations

The timespan between measurements in the study may have influenced results, with transient health effects emerging and resolving within the two years before follow-up not detected. Effect estimates in the present study may be underestimated due to inherent limitations of estimating complex processes at discrete time points. Furthermore, clinically relevant mental distress was identified by a cutoff criterion (34), leaving health effects at the subclinical levels undetected and effects underestimated. Although clinical cut-off is a strict criterion, we utilized this in order to identify work exposures, which may have profound impact on employee functioning and quality of life both at and outside of work. This is especially pertinent given the current challenge of mental illness being one of the lead- ing causes of disability, sick leave, and production losses (12). Not adjusting for type of job contract may also have influenced results as one might speculate type of contract to be associated with differences in job predictability (45). Sample composition and self-selection may also have influenced results as organizations were invited to sign up for participation themselves.

Attrition analyses linked lower job predictability to dropout, which may compromise the generalizability of the results. Employees working in professions requiring <15 years of formal education were also less likely to participate at follow-up. These are also the professions reporting the lowest job predictability and future employability and which seem the most affected by technological innovations such as automatization (12). We conducted a post-hoc random intercept linear regression analysis to examine the associations between skill level and job predictability and future employability. These results showed workers employed in professions requiring <15 years of formal education reported significantly lower levels of job predictability and future employability (supplementary table S6). Thus, at follow-up, there was a significant drop in responses from the group of workers potentially most affected by the structural changes in modern day work life.

Employees suffering from mental distress at baseline may experience their own future as more uncertain, hence reverse causality may be present. A set of post-hoc random intercept linear regressions were run to assess the prospective associations of clinically relevant mental distress and job predictability and future employability. The results showed mental distress to be associated with lower levels of job predictability and future employability at follow-up (supplementary table S7), hence reverse causality may be present at the individual level. However, prospective analyses adjusting for baseline levels of the outcome should be less sensitive to reverse causality bias as the association of the outcome with the exposure at baseline is partialled out. At work-unit level, reverse causality is less likely even when not baseline adjusted due to the aggregated predictor. Furthermore, perceived predictability and employability possibly influence employees' ratings of superiors. Present posthoc analyses showed baseline

levels of predictability to predict perceived leadership behaviors (supplementary table S8). Future studies assessing the effects of job predictability and leadership may explore this further.

As data were collected by questionnaires, common method and reporting biases may have influenced results (46). However, the multilevel approach should diminish the influence of such bias as responses are aggregated at the work-unit level, which minimizes the effect of individual response bias (35, 39). Moreover, it is equally important to be aware that non-significant effects at the work-unit level do not prove the existence of reporting bias at the individual level, as some relationships are primarily individual-level phenomena. Non-significant effects at work-unit level may also be due to significantly fewer observations at this level, which attenuates the statistical power (47). The question also remains whether the unit of aggregation is appropriate for the phenomena in question, as different characteristics of work may be shared at different levels, such as, eg, work unit, organization, or job type.

Future perspectives

The present results show uncertainty regarding one's present and future job prospects may affect mental health to the extent of clinical relevance. In order to alleviate the straining effects of low predictability, identification of protective factors is essential. Although the present results did not show a moderating effect of leadership behaviors on the effect of job predictability on mental health, a direct effect at both individual- and work-level was shown. The present results suggest that leadership behaviors might be a relevant factor in preventing mental distress, possibly by reducing both short- and long-term uncertainty in the workplace.

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Sidebar

The paper utilizes a multi-level approach to elucidate the potential cross-level moderating effects of various leadership behaviours on the relationship between job predictability and future employability and employee mental health. No moderating effects were found, however, an individual- and cross-level direct effect of all included leadership behaviours was shown, underlining the importance of such leadership in securing employee mental health.

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Additional material

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DETAILS

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Risk of work-related hand eczema in relation to wet work exposure

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ABSTRACT (ENGLISH)

Objective Albeit a pivotal risk for the development of hand eczema (HE), the exposure-response relationship between wet work and HE remains to be further investigated. Knowledge on exposure-response is important regarding preventive measures, medico-legal regulations and job-counseling. Recently, a job-exposure matrix (JEM) for wet work was developed, providing information on the likelihood of wet work. By combining the JEM with data on HE we aimed to investigate the relationship between extent of wet work and HE. Methods This study is a case-referent study including patients registered in the National Database of Contact Allergy, Denmark, and comprises data on sex, age, atopic dermatitis, HE, face eczema and patch testing results. Patients with HE served as cases and patients with facial eczema served as referents. Information on profession was retrieved from the DOC·X database in accordance with the DISCO-88 classification system. A wet-workspecific JEM provides - for each profession - an estimate for (i) the likelihood of wet work lasting ≥2 hours/day and (ii) the average number of hours of wet work per day. Results After two hours of wet hands and glove wear, the odds ratio (OR) was 3.49 and 3.19, respectively, for females and 2.41 and 1.82, respectively, for males. Females had a higher risk of HE than males with probability of wet hands <75% (OR 2.34, 95% CI 2.12-2.58 compared to males 1.68, 95% CI 1.22-2.31) and regarding glove wear at all exposure levels. Conclusion Our data confirms a close association between wet work and HE. Exposure lasting less than the current definition of wet work (having wet hands for ≥2 hours per day) may be of importance.

FULL TEXT

Headnote

Objective Albeit a pivotal risk for the development of hand eczema (HE), the exposure-response relationship between wet work and HE remains to be further investigated. Knowledge on exposure-response is important

regarding preventive measures, medico-legal regulations and job-counseling. Recently, a job-exposure matrix (JEM) for wet work was developed, providing information on the likelihood of wet work. By combining the JEM with data on HE we aimed to investigate the relationship between extent of wet work and HE.
Methods This study is a case-referent study including patients registered in the National Database of Contact Allergy, Denmark, and comprises data on sex, age, atopic dermatitis, HE, face eczema and patch testing results. Patients with HE served as cases and patients with facial eczema served as referents. Information on profession was retrieved from the DOC·X database in accordance with the DISCO-88 classification system. A wet-workspecific JEM provides - for each profession - an estimate for (i) the likelihood of wet work lasting ≥2 hours/day and (ii) the average number of hours of wet work per day.
Results After two hours of wet hands and glove wear, the odds ratio (OR) was 3.49 and 3.19, respectively, for females and 2.41 and 1.82, respectively, for males. Females had a higher risk of HE than males with probability of wet hands <75% (OR 2.34, 95% CI 2.12-2.58 compared to males 1.68, 95% CI 1.22-2.31) and regarding glove wear at all exposure levels.
Conclusion Our data confirms a close association between wet work and HE. Exposure lasting less than the current definition of wet work (having wet hands for ≥2 hours per day) may be of importance.
Key terms contact dermatitis; dermatitis; DOC·X; JEM; job exposure matrix.
Key terms: contact dermatitis; dermatitis; DOC·X; eczema; exposure; hand eczema; JEM; job exposure matrix; wet work
Wet work is one of the strongest known risk exposures for the development of work-related hand eczema (HE) (1-3), which is ranked among the top notified occupational diseases in several European countries, revealing a large potential for successful prevention strategies (3-6). Although wet work is a pivotal risk factor for developing work-related HE, the exposure-response relationship between extent of wet work and development of work-related HE remains to be further investigated (7, 8). Prior studies have shown that decreasing intensity or ceasing wet work has a significantly positive effect on the severity of work-related HE (9, 10). The definition of wet work as having wet hands for >2 hours per working day, hand washing >20 times per working day, or wearing occlusive gloves for >2 hours per working day is widely accepted; however, it does not take into account variations related to occupations or sex (11). Assuming a specific level of exposure representing an entire specific profession may disregard considerable individual variations among job tasks and sex. The variation among exposure levels between females and males have been documented in several studies, where females are exposed to higher levels of wet work than their male colleagues (12-14).
Variations in duration and frequency of wet work activities has been studied in specific wet work occupations, such as hairdressers, cleaners and health care workers; however, there are few studies regarding doseresponse relationship (7, 10, 15-22). Knowledge on exposure-response is important regarding specific preventive measures, and also in relation to medico-legal regulations and individual job-counseling. Recently a job-exposure matrix (JEM) for wet work has been developed, providing information on the likelihood of wet-work activity (23). By combining data from the JEM with data on HE, in this study we aim to investigate the relationship between extent of wet work and diagnoses of HE.

Methods

Study population

This study is a case-referent study including patients registered in the National Database of Contact Allergy, Denmark (24). The database was founded in October 2002 and comprises data from patients who have been patch tested at a varying number of dermatological hospital departments (N=3-5) and private dermatology practices in Denmark (N=7-13). Data in this study covers the period 1 January 2003 to 31 December 2015. Data registered in the database comprise sex, age, status of atopic dermatitis (current or previous), HE, face eczema as well as result of patch testing (positive or negative). Patients identified with HE served as cases, and patients identified with face eczema served as referents.

Assessment of profession

Information on profession was retrieved from the DOC·X database at Statistics Denmark (25). The database covers all employed Danish citizens from the age of 15 years and comprises information regarding annual status of profession, educational level, income level, resident children <4 years of age and, residence (25). Data on profession is categorized in accordance with the Danish DISCO-88 classification system based on the four-digit International Standard Classification of Occupations (ISCO)-88 classification system. Data from the National Database of Contact Allergy, Denmark, was linked at the individual level with data from the database DOC·X at Statistics Denmark using the Danish personal identification number (20), and the registered profession from the year prior to being included in the database was used. Likelihood of smoking was estimated based on a sex, age and calendar year specific JEM addressing lifestyle factors, such as tobacco smoking (26).

Exposure assessment

Exposure to wet-hand activities was assigned by a wetwork-specific JEM, based on a self-reported question about wet-hand activity from national surveys on working environment performed by the National Research Centre for the Working Environment in Denmark in 2000, 2005, and 2010 (National Research Centre for the Working Environment) (23). In the JEM, wet hands are defined as having wet or moist hands, and glove wear is defined as wearing protective gloves made of plastic or rubber. The JEM is based on 432 professions classified according to the DISCO-88 system and provides both an estimate for the likelihood of having wet hands or wearing gloves >2 hours/day for each profession and an estimate of the average number of hours per work day (8 hours) having wet hands/wearing gloves, respectively. Both variables are calculated for working hours only and do not include leisure-time activity. The estimates were calculated for each of the 432 professions by fitting a logistic model in SAS V.9.4 (SAS Institute, Cary NC, USA). For the purpose of this study, we linked estimates from the JEM to each individual in the study population by the DISCO-88 code from the DOC·X database.

Outcome assessment

Outcome data included diagnosis of HE from the National Database of Contact Allergy, Denmark. Differentiation between different subgroups of HE is not considered. The database has patients registered in the MOAHLFA index (27) by dermatologists only, thus the diagnose of HE is assumed to be precise and reliable.

Statistical analysis

Before performing any analysis, patients with combined HE and facial eczema were excluded (figure 1). Crude and adjusted risk for HE according to wet-work exposure were computed by logistic regression, that also provides 95% confidence intervals (CI). In the analysis, likelihood of wet-work exposure for >2 hours per work shift was divided in four groups (0-25, >25-50, >50-75, >75%). We did equal analyses with the exposure variable "glove wear". We furthermore performed the analyses stratified by sex. In the main analyses, we adjusted for sex (1=male, 2=female), age (1=<30, 2=30-39, 3=40-49, and >50 years), educational level (1=primary school, 2=upper secondary education, 3=vocational upper secondary education, 4=medium-cycle higher education, and 5=long-cycle higher education), income level (1=low, 2=medium, 3=high, and 4=very high), resident children <4 years of age (0=no, 1=yes), residence (1=Copenhagen area, 2=Zealand, 3=Funen, 4=Jutland) atopic dermatitis (0=no, 1=yes) and result of patch test (0=no, 1=yes). We also adjusted for smoking by use of a smoking JEM with estimates of likelihood of being a smoker (%) for each DISCO-88 code. The group-based estimates were linked to each individual in the study population by the same DISCO-88 group as the group classifying the wet exposure likelihood. The smoking JEM is described elsewhere (26).

Tables 2a, 2b and 2c, present crude and three analyses adjusted, respectively, for (i) all potential confounders, (ii) only demographic (sex, age, resident children <4 years), and (iii) both demographic and socio-economic (education, income, residence and smoking).

A supplementary logistic regression analysis model with exposure as average hours per working day modelled as a natural spline with three knots was used when graphically illustrating the dose-response relationship between number of estimated average daily exposure hours from the JEM and risk of HE for the outcomes "wet hands" and "glove wear", respectively. All analyses were performed in SAS version 9.4. A significance level of 0.05 was used throughout.

Results

In our final study population (N=49 706), 11 706 had been diagnosed with solely HE and 5499 with solely facial eczema (figure 1). Information regarding wet hands was available for 17 205 individuals and regarding glove wear on 15 241, both attained by linkage with the JEM. Table 1 presents demographic characteristics of HE and facial eczema patients, respectively. The characteristics of patients with HE or facial eczema were rather similar, with sex distribution differing the most; 63.7% of HE patients were female compared to 81.0% of facial eczema patients. More HE patients had resident children <4 years, a lower proportion of atopic dermatitis, lower level of education and lower proportion of very high income level.

The odds ratios (OR) for having HE based on having wet hands or wearing gloves - both measured as probability of >2 hours per working day - are presented in table 2. HE was significantly related to both wet-work activities (wet hands and glove wear), and the significant association increased concurrently with likelihood of wet work. With >75% probability of wet hands, the OR was 2.97 (95% CI 2.57-3.43) compared to OR 1.44 (CI 1.30-1.60) with >25-50% probability of wet hands. With >75% probability of glove wear, the OR was 2.50 (95% CI 2.20-2.85) compared to OR 1.72 (95% CI 1.53-1.93) with >25-50% probability of glove wear (table 2a). As shown in tables 2b and 2c, females had higher risk of HE compared to men when probability of wet hands was <75% (males OR 1.68, 95% CI 1.22-2.31 compared to females' OR 2.34, 95% CI 2.12-2.58), but males had higher risk of HE compared to females when probability of wet hands was >75% (males OR 3.52, 95% CI 1.76-7.05 compared to females OR 2.95, 95% CI 2.54-3.43). This concerns both crude and adjusted analyses. Regarding glove wear, females had higher risk of HE compared to men at all levels of glove wear when compared to the reference group.

Figure 2 illustrates the dose-response relationship between amount of wet hands (average hours as a continuous measure) and risk of HE in females and males. OR for having HE doubled after 39 minutes for females and after 77 minutes for males. After two hours, the OR was 3.49 for females and 2.41 for males. Similarly, dose-response for the association between glove wear (average hours as a continuous measure) and risk (OR) of HE in females and males is illustrated in figure 3. Regarding exposure to glove wear, OR for having HE doubled after 27 minutes for females and after 55 minutes for males. After two hours OR was 3.19 for females and 1.82 for males.

Discussion

Overall, we found OR of having HE significantly related to the extent of wet work, particularly among females. Dose-response curves for average time with wet hands and glove wear at work illustrated that OR for having HE doubled for both sexes earlier than the current definition of wet work >2 hours.

The risk of having HE in professions where 25-50% of workers are exposed to wet hands >2 hours/day was significantly increased and increased further in professions where 50-75% and 75-100% of workers are exposed to wet hands >2 hours/day. While the definition of wet work is widely accepted, and a clear association between wet work and HE is well established (7, 9, 10, 28-30), quantitative data on the dose-response relationship is sparse. Prior studies that have investigated the effect of water exposure to the skin, have shown that daily water exposure <1 hour/day does not irritate the skin (29, 31). Although based on small samples (N=21), in vitro pig skin and in vivo human skin, these findings may be used to support the present definition of wet work >2 hours/day in relation to HE, but no other studies have to our knowledge shown specific levels of cut-off. When adjusting for possible confounders such as age and atopic dermatitis, the risk of having HE for both females and males remained regarding wet hands (table 2a). However, when assessing the risk separately for males and females regarding glove wear (tables 2b and 2c), it becomes evident that the pattern differs for males, where we find that widespread use of gloves is not related to a significant increased risk of HE (Figure 3). The difference between the various confounder adjustments is that patch test and atopic dermatitis, do not seem to have much impact on risk of HE. These findings point towards that wet work is an independent risk factor of HE. Adjusting for socioeconomic confounding attenuates risks somewhat, though when taking uncertainties in the analyses into account this does not change conclusions. Impact of confounding is similar in the sex stratified analyses.

In some male dominated professions, for example masonry and painting, a large number of workers wear non-occlusive gloves or a mix of occlusive and nonocclusive gloves. Despite the phrasing of the question regarding glove

wear, including only occlusive glove material (plastic, rubber), a possible explanation for the difference between males and females may be that the question was understood to include gloves in general, thereby affecting responses from men more than women and resulting in a not-so-straightforward interpretation. Glove wear may also be for the protection against mechanical exposure, which was not investigated in this study. In this case, increased glove wear does not indicate increased wet work and the risk of HE (due to wet work) no longer applies.
Whether glove wear constitutes a risk exposure or a protective factor is still under discussion, and there are several studies with results pointing in both directions (32-37). Due to the present definition of wet work, where glove wear is included, we have chosen to maintain it as a such in our study.
Our findings illustrate that the risk of HE also increases when performing wet work <2 hours per day on average, which is the timeframe defining wet work today (figure 2) (11). This represents a current risk of overlooking both specific wet-work tasks as well as specific wet-work professions where this time definition of >2 hours/day is not obtained, but which however may still lead to HE. Our results were most significant for females, confirming previous studies describing the risk profile of wet-work professions (2, 10, 14, 38). A biological difference such as a higher susceptibility in female skin sensitivity has been excluded in several studies (39, 40), and the increased risk of HE found in females may therefore be solely related to exposure (41, 42).
Strengths and limitations
To the best of our knowledge, this is the first study to present an exposure-response relationship between extent of wet work and the diagnosis HE. One of the strengths of our study is that it is based on independent sources of data, minimizing the risk of recall bias. We have been able to further strengthen this study with a recently developed wet-work-specific JEM, based on large nationwide representative survey data with a high participation rate (23). The group of patients comprising the case-referent population are appropriate for our aim due to the availability of both a HE diagnosis and patch test results, the latter to be used when checking for confounding. The risk of misclassification bias regarding validity of diagnoses is assumed to be low as a dermatologist diagnosed both the HE and facial eczema, and consequently also the absence of having HE. Although possible differential diagnosis does exist, this will only count for a few cases. Nevertheless, it is acknowledged that the validity of the diagnoses in the National Database of Contact Allergy has not been explicitly documented. The number of missing data on profession in this population was low, which further strengthens the study. We chose to use DISCO-codes from the year previous to the year of patch testing. The choice was based on the assumption that a high probability of workers either were in the same position the year of patch testing as the year before or a position in the same occupational category. This choice may have led to misclassification bias regarding workers who may have changed profession resulting in a likely attenuated estimate of the actual risk. The independent sources of data based on large and broad survey data strengthen the external validity of this study.
Apart from occupational exposure, the importance of wet work at home has been discussed in earlier studies (43, 44), and a positive relationship between occupational wet-work exposure and wet work at home has been found (22, 45) We accounted for this aspect by adjusting for resident children <4 years of age. However, information on other activities such as certain leisure activities eg, fishing and gardening were not accessible. Adjusting for confounding by socio-economic factors (residence, income level, educational level) tended to attenuate risk estimates, which might in part be explained by difference in health seeking behavior.
Other possible confounders of interest are some lifestyle factors. Tobacco smoking is a risk factor for HE with a strong gradient across professions and thus a likely important confounder (24). We accounted for confounding by smoking by use of a sex-, age- and calendar-time specific JEM which in large national samples predicts all-cause mortality and acute myocardial infarction independently of other risk factors (26, 46). In addition to tobacco smoking, which have been included as JEM-based estimates, other lifestyle factors such as exercise and level of stress could be of interest (47, 48).
Misclassification of exposure may arise when the average exposure at the group level is assigned to all individuals belonging to the group. This occurs when exposure data is based on a JEM, which per definition does not reflect any variation among individuals working in the same profession. The consequence of non-differential misclassification of

exposure may be attenuated risk estimates which first of all is a problem in JEM based studies that contrary to our study are presenting null findings. However, to the extent that that the assigned average JEM-based values are valid, groupbased exposure assessment is likely predominantly to be associated with a Berkson-type of error rather than a classical error which tends to have unbiased or lessbiased associations but wider CI (49-51).
The potential risk of classifying exposure levels into broad groups is that we assume equal risk within these groups, which may underestimate the OR. However, our analysis of time of exposure is based on continuous exposure data and reaffirms the overall conclusions that increased exposure increases the risk of hand eczema.
In a recently published study comparing self-reported data to observational data on wet work (21), we found that professions with high wet-work prevalence overestimated duration of wet-work activities. This finding is in accordance with Jungbauer et al (15) and Anveden et al (17), who also found duration of wet work to be overestimated in self-reported studies. Future studies could consider that the increased risk of HE may occur at much shorter durations of wet work than our data show. This could support an even more restrictive approach towards possible legislation in the area of prevention of HE.
Concluding remarks
Dose-response curves for wet work showed a significant risk of having HE even at an exposure level of <30 minutes on average of wet work/day. Our data confirmed a close association between wet work and HE and illustrated that exposure lasting less than the current definition of wet work (>2 hours) may be of importance. Based upon the results of this study, this definition may need to be reevaluated.
Females had higher risk of HE compared to men when probability of having wet hands was <75%, but males had higher risk of HE compared to females when probability of wet hands was >75%
Regarding glove wear, females had higher risk of HE compared to men at all levels of glove wear when compared to the reference group.
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The authors have no interests to declare.
Sidebar
This study is the first to describe a dose-response relation between the risk of having hand eczema and duration of wet work (wet hands or occlusive glove wear).
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DETAILS

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Shift work and use of psychotropic medicine: a follow-up study with register linkage

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ABSTRACT (ENGLISH)

Objective This study aimed to investigate a prospective association between shift work and use of psychotropic medicine. Methods Survey data from random samples of the general working population of Denmark (N=19 259)

were linked to data from national registers. Poisson regression was used for analyses of prospective associations between shift work and redeemed prescriptions of psychotropic medicine. Prevalent cases were excluded at baseline. In secondary analyses, we tested differential effects on subsets of psychotropic medicine and, crosssectionally, we studied correspondence between estimates based on psychotropic medicine and self-reported mental health. According to the protocol we interpret results from the secondary analyses following the principles for nested hypothesis testing, if the primary analyses reject the null-hypothesis, and otherwise we regard it as hypothesis generating exploratory analyses. Results In the primary analysis, the rate ratio for incidence of psychotropic medicine among shift workers was 1.09 (95% confidence interval 0.99-1.21). Results from the secondary analyses suggested increased incidence of use of hypnotics, sedatives and antidepressants and decreased incidence of use of anxiolytics. Cross-sectional analysis suggested increased risk for use of psychotropic medicine (all kinds), but not for poor self-rated mental health. Conclusions Results did not support that working in shifts to the extent that is currently practiced in Denmark is associated with an increased incidence of overall psychotropic medicine use. Future studies should test, whether there is a differential incidence for different drugs among shift workers as suggested by the secondary analyses and how psychotropic medicine use and mental health are related.

FULL TEXT

Headnote

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Key terms antidepressant; anxiolytic; mental health; prescription drug; occupational health; sedative; shift worker.

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Shift work is related to disturbances in the circadian rhythm and sleep disturbances, which are suspected to contribute to mental health problems (1-4). A metaanalysis of 11 primary studies concluded that night shift work was significantly associated with an increased risk of depression (5), and a prospective study found a flexible/non-regulated schedule prospectively associated with antidepressant prescription among females (6). Other prospective studies have not found shift work associated with the development of mental health problems (7, 8) nor with use of psychotropic drugs (9-11). Thus, it is essential to investigate the possible negative effects of shift work on mental health.

There may be different mechanisms behind a possible association between shift work and mental health. Circadian misalignment may disrupt the internal synchronization of the hypothalamic-pituitary-adrenal (HPA) axis, that is

responsible for several neurotransmitters and hormones (1). In turn this may lead to abnormal responses to stress. And together with sleep disturbances, the stress responses may affect mood, and vigilance (12), and as such the regulation of emotions (1). Shiftwork is furthermore known to have negative impact on work-life balance, social life issues (13, 14) and on marital satisfaction (15). And beside this, some of the occupational sectors where shift work is prevalent, eg, healthcare and protective services, are also sectors chracterized by increased risk for exposure to traumatic events (16, 17). Thus, biological as well as social and environmental factors may interact as under lying mechanisms behind an association between shift work and mental health.

The aim of the present study was to assess if shift work is associated with increased risk of psychotropic medicine use. Firstly, we investigated the prospective association between shift work and incident use of psychotropic medicine. Secondly, we tested differential prospective effects on subsets of psychotropic medicine. Thirdly, in order to evaluate whether prescription bias was present, we related the association between shift work and self-rated mental ill health and medicine use, respectively.

Methods

The data material, the hypotheses and the statistical methods of the study were defined, peer-reviewed and published in a detailed study protocol (18), before we performed the linkage between the exposure and the outcome data of the study. For information about the data material and statistical methods and models see Hannerz &Albertsen (18, 19). Only a brief description of the data and methods will be given here.

Data material

The data material was obtained through a linkage of survey data from the Copenhagen Psychosocial Questionnaire study (COPSOQ) sample of 2004, the Danish National Working Environment Survey (DANES) of 2008, and the Danish Work Environment Cohort Study (DWECS) of 1995, 2000, 2005, and 2010 with data from the Central Person Register, the Employment Classification Module, and the Danish National Prescription Registry (DNPR). The COPSOQ study sample is a random sample, which comprises 4732 people, 20-59 years of age, whereof 3517 are wage earners (20). DANES is based on a random sample of the Danish population in 2008. It comprises responses from 6531 persons 18-59 years of age, of which 4919 are employees. The DWECS is an open cohort study, based on a random sample of people 18-59 year of age in the Danish population. The cohort contains a representative cross-sectional datacollection among at least 5000 employees every fifth year from 1990-2010 (21).

Primary analysis

Case definition. A person was defined as a case if and when he or she redeemed a prescription for drugs in the anatomical therapeutic chemical (ATC) code category N05 [psycholeptica=antipsychotics (N=58), anxiolytics (N=495), hypnotics and sedatives (N=752)] or N06 [psychoanaleptica=antidepressants (N=941), psychostimulants (N=12) and anti-dementia drugs (N=0)]. In addition, 656 cases received combinations of different drugs. In total there were 2914 cases. For specification of this see (19).

Follow-up and inclusion criteria. Each of the included samples was followed for a period of 2-5 years (depending on the time available between the sampling and the end of the study period, 31 December 2012) beginning at the start of the calendar year succeeding the one in which they were sampled. Participants who redeemed a prescription for a medication with an ATC-code that belong to the case definition, during the calendar year preceding baseline (prevalent cases) were excluded from the follow-up. Participants could participate in several rounds. A participant who reached the clinical endpoint of the study was not allowed to re-enter the follow-up, ie, there would be maximum one case per person. People aged 21-59 years at the start of the follow-up period and employed >32 weekly working hours around the time of the interview were included [for further information see (18)].

Exposure assessment. The surveys contain information on the participants' normal work schedules. The questions and response categories vary slightly between the questionnaires, but all of them can identify workers who are either on fixed night shifts or rotational shift work schedules (see supplementary material, www.sjweh.fi/show_abstract.php?abstract_id=3872, appendix 1 and 2).

Statistical model. Poisson regression was used to model incidence rates of redeemed prescriptions for psychotropic medicine as a function of currently working in shifts (permanent night shifts, rotational shift work schedules (both

with and without night shifts) or irregularly placed hours versus permanent day, morning or evening). The analysis was adjusted for sex, age (10-year classes), sample (DWECS 1995; DWECS 2000; COPSOQ 2004; DWECS 2005; DANES 2008; DWECS 2010), weekly working hours (32-40, 41-48, >48 hours/week) and socioeconomic status. The logarithm of person years at risk was used as offset. The significance level was set to 0.05. A likelihood ratio test was used to test the null hypothesis.

Secondary analyses

As described in the protocol (18), we performed a series of secondary analyses (for results from all analyses see appendix 3). Sensitivity analyses were performed in the same way as we did in the primary analysis, but with endpoints defined by the subsets of N05B (anxiolytics), N05C (hypnotics and sedatives), and N06A (antidepressants). In order to evaluate whether prescription bias was present, we compared the association between shift work and self-rated mental ill health (MHI-5; cut-off: 52 points) with the association between shift work and redeemed prescriptions. Logistic regression was used to model the odds of outcomes in cross-sectional analyses. The analyses were adjusted like in the primary analysis. In the protocol (18) it was described that interpretation of results from the secondary analyses would follow the principles for nested hypothesis testing, if the primary analyses rejected the null-hypothesis and otherwise, they would be regarded as hypothesis generating exploratory analyses.

Results

In the primary analysis, the inclusion criteria for age, employment status and working hours were fulfilled for 29 837 observations. Of these, we excluded 3084 due to prior redeemed case prescriptions, and 794 due to missing data on shift work, which left us with 25 959 observations (19 259 persons) to be included in the analysis. The included observations yielded a total of 2914 new cases of psychotropic drug use in 99 019 person years at risk. For details of each of the included data sets see (19).

In the prospective analysis, we found no overall increased risk for incidence of psychotropic drug use among shift workers compared to fixed day workers (P=0.09). Thus, the likelihood ratio test did not reject the null hypothesis. The estimated rate ratio, person years at risk and number of cases are given in table 1.

In the sensitivity analysis (see table 2), we observed higher incidence for hypnotics and sedatives and antidepressants, and lower incidence for anxiolytics.

The cross-sectional analysis showed that working in shifts was associated with an increased propensity to redeem prescriptions for psychotropic drugs, but not with an increased tendency to report poor mental health (see table 3).

Discussion

In the primary analysis, we did not find a statistically significant association between shift work and the incidence of psychotropic drug usage (all types combined) among Danish employees. Given that this study had enough power to detect an effect, the primary results support a conclusion saying that working in shifts to the extent that is currently practiced in Denmark is not associated with an increased incidence of overall psychotropic medicine use. The overall result is in line with findings from other prospective studies that did not find work in shift associated with development of mental health problems (7, 8) or with use of psychotropics (9-11). As mentioned in the introduction, some previous prospective studies have found associations between shift work and psychotropic drug usage. However, one of these studies (6) was based on analyses with rather low statistical power and multiple tests, of which only one reached significance. The other (5) only included two prospective studies in a meta-analysis - one of which was severely underpowered and the other reported in an untransparent way without inclusion of the prospective findings. The authors recommend studies with stronger designs in order to draw confirmative relationships.

It is important to notice that results from this study do not address whether working in shifts for some people may be contraindicated due to the experience of mental health problems (eg, serious sleeping problems). In line with the findings of this study, results from a large nonrandomized pseudo-trial from Finland (22) showed no increased risk of developing common mental disorder after changing from non-night to night work. The authors found, however, (i) increased likelihood of recovery from common mental disorder if night workers changed from night- to non-night work and that (ii) night workers were more likely to change to non-night work if they had developed common mental

disorder. Thus, the selection out of night work may be dependent on the individuals' experience of mental health problems (including sleeping disorders). Thus, employees whose mental well-being is affected are likely to change their schedules to day work, and this change is - in turn - likely to help them recover from the common mental disorder.

Results from the secondary analyses suggested increased incidence for the use of hypnotics, sedatives, and antidepressants and decreased incidence for the use of anxiolytics among shift workers. A simple interpretation of the differential effects may be that it was a coincidence. Another interpretation could be that shift work increases the incidence of sleeping problems and depression and decreases the incidence of anxiety. These oppositely directed effects cancel out each other and give a non-significant total effect. If this interpretation is right, different incidences of diagnoses among shift workers versus others should be hypothesized. Both interpretations should be tested in future studies by including both several psychotropic drugs and diagnoses as outcomes. A third interpretation could be that there are different practices for prescription of psychotropics to people working in shifts compared to non-shift workers. The general practitioner may decide the specific medication for mental health and sleeping problems among people working in shifts taking into consideration the requirement of often being awake and not being too tired at night and being able to sleep during the day. As one of the side-effects of anxiolytics may be drowsiness, it is likely that the general practitioner will rather prescribe antidepressants over anxiolytics to people working in shifts and suffering from anxiety. This interpretation will get support if studies find no difference in diagnoses of depression and anxiety among shift workers versus non-shift workers. Results from a survey on the use of psychotropic medication in the general populations of France, Germany, Italy, and the United Kingdom lend support to this interpretation: "Subjects said that they were taking an antidepressant to reduce depression in 30.7% of cases; 25.5% said it was to help them to sleep; in 24.5% it was to reduce anxiety; and in 13.4% it was to help them to sleep and to reduce anxiety and depression" (23). Thus, the prescription of psychotropics is not always specific for specific sufferings.

Cross-sectional results suggested increased prevalence of psychotropic drug use but not poor mental health among shift workers. These results may reflect that the medication has had a positive effect on the perception of mental health. Therefore, we cannot be sure whether the increased prevalence of drug use was due to an increased need of treatment for mental health problems or an increased propensity to seek treatment (eg, for sleeping problems). We can only conclude that the two outcomes give different estimates of risk. As suggested above, future studies may also shed more light on possible prescription bias. Clarifying the relation between shift work and changes in mental health and drug use would probably require frequent follow-up on both outcomes or more clinical studies.

Strengths and weaknesses

Within-study selection bias was eliminated through our study protocol, in which hypotheses and statistical models were specified, peer reviewed, and published before the questionnaire data were linked to the registers. The study population was randomly sampled from the target population and the statistical power was sufficiently large to detect important effects. The problem with reversed causality was minimized through the prospective design and the exclusion of prevalent cases. Bias from incomplete follow-up data was eliminated by use of a clinical endpoint that was ascertained through national registers, which cover all residents of the target population. As suggested by results from previous research, selection processes into (24) as well as out of shift work (22) are likely, and perception of mental health and sleep quality may play a role in both selection processes. A limitation of the study was that it included neither measures of the length of exposure or previous daytime work among the shift workers nor previous shift work among the non-shift workers. Due to this limitation, the results cannot rule out a potential dose-response effect of shift work on mental health. For further methodological considerations see (19).

Concluding remarks

Results did not support that working in shifts - to the extent that is currently practiced in Denmark - is associated with an increased incidence of overall psychotropic medicine use. Future studies should test whether there is a differential incidence for different drugs among shift workers as suggested by the secondary analyses and if there is prescription bias for the outcome of psychotropic medicine.

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Conflicts of interests
The authors declare no conflicts of interest.
Ethics approval
The study will comply with The Act on Processing of Personal Data (Act No. 429 of May 31, 2000), which implements the European Union Directive 95/46/EC on the protection of individuals.
Sidebar
Results supported that working in shifts to the extent that is currently practiced in Denmark is not associated with increased incidence of overall psychotropic medicine use. Future studies should test whether there is a differential incidence for different drugs among shift workers as suggested by the secondary analyses and whether there is prescription bias for the outcome of psychotropic medicine.
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Inpatient multimodal occupational rehabilitation reduces sickness absence among individuals with musculoskeletal and common mental health disorders: a randomized clinical trial

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ABSTRACT (ENGLISH)

Objectives This study aimed to investigate whether inpatient multimodal occupational rehabilitation (I-MORE) reduces sickness absence (SA) more than outpatient acceptance and commitment therapy (O-ACT) among individuals with musculoskeletal and mental health disorders. Methods Individuals on sick leave (2-12 months) due to musculoskeletal or common mental health disorders were randomized to I-MORE (N=86) or O-ACT (N=80). I-MORE lasted 3.5 weeks in which participants stayed at the rehabilitation center. I-MORE included ACT, physical exercise, work-related problem solving and creating a return to work plan. O-ACT consisted mainly of 6 weekly 2.5 hour group-ACT sessions. We assessed the primary outcome cumulative SA within 6 and 12 months with national registry-data. Secondary outcomes were time to sustainable return to work and self-reported health outcomes assessed by questionnaires. Results SA did not differ between the interventions at 6 months, but after one year individuals in I-MORE had 32 fewer SA days compared to O-ACT (median 85 [interquartile range 33-149] versus 117 [interquartile range 59-189)], P=0.034). The hazard ratio for sustainable return to work was 1.9 (95% confidence interval 1.2-3.0) in favor of I-MORE. There were no clinically meaningful between-group differences in self-reported health outcomes. Conclusions Among individuals on long-term SA due to musculoskeletal and common mental health disorders, a 3.5-week I-MORE program reduced SA compared with 6 weekly sessions of O-ACT in the year after inclusion. Studies with longer follow-up and economic evaluations should be performed.

FULL TEXT

Headnote

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Methods Individuals on sick leave (2-12 months) due to musculoskeletal or common mental health disorders were randomized to I-MORE (N=86) or O-ACT (N=80). I-MORE lasted 3.5 weeks in which participants stayed at the rehabilitation center. I-MORE included ACT, physical exercise, work-related problem solving and creating a return to work plan. O-ACT consisted mainly of 6 weekly 2.5 hour group-ACT sessions. We assessed the primary outcome cumulative SA within 6 and 12 months with national registry-data. Secondary outcomes were time to sustainable return to work and self-reported health outcomes assessed by questionnaires.

Results SA did not differ between the interventions at 6 months, but after one year individuals in I-MORE had 32 fewer SA days compared to O-ACT (median 85 [interquartile range 33-149] versus 117 [interquartile range 59-189)], P=0.034). The hazard ratio for sustainable return to work was 1.9 (95% confidence interval 1.2-3.0) in favor of I-MORE. There were no clinically meaningful between-group differences in self-reported health outcomes.

Conclusions Among individuals on long-term SA due to musculoskeletal and common mental health disorders, a

3.5-week I-MORE program reduced SA compared with 6 weekly sessions of O-ACT in the year after inclusion. Studies with longer follow-up and economic evaluations should be performed.
Key terms cognitive behavioral therapy; fatigue; health services research; inpatient care; musculoskeletal diseases; occupational rehabilitation; physical exercise; problem solving; psychiatry; return to work.
Key terms: cognitive behavioral therapy; fatigue; health services research; inpatient care; inpatient multimodal occupational rehabilitation; mental health; mental health disorder; musculoskeletal disease; musculoskeletal disorder; occupational rehabilitation; physical exercise; problem solving; psychiatry; randomized clinical trial; return to work; sickness absence

Musculoskeletal and common mental health disorders are the major causes of disability and working years lost in the western world (1-4). For musculoskeletal disorders, effective occupational rehabilitation programs have comprised multimodal interventions including components such as physical exercise, psychological/ behavioral therapy, work-related problem solving and often involvement and coordination of different stakeholders (5, 6). For individuals with musculoskeletal or common mental health disorders, a recent meta-analysis concluded that psychological treatments reduce sick leave more than usual care, albeit with small effect sizes, and inconclusive results as to which form of psychological treatment is the most effective (7).

The worker's decision to remain off or return to work involves complex interactions between personal beliefs, physical, psychosocial, and system factors and goes far beyond the medical treatment paradigm for any specific diagnosis (8, 9). In addition, co-morbidity between musculoskeletal pain and mental health disorders is high (10-12). Successful occupational interventions for individuals with musculoskeletal disorders have recently inspired the development of similar promising interventions for common mental health disorders (5, 13).

Acceptance and commitment therapy (ACT) is a recent development within cognitive behavior therapy with empirical support as a coping strategy for a broad range of clients (14), including for individuals with musculoskeletal and common mental health disorders (15-17). A Swedish randomized pilot study reported fewer sickness absence (SA) days in women with musculoskeletal complaints receiving ACT (18). Furthermore, ACT has successfully been implemented as a coping modality in group-based interventions for sicklisted individuals with different diagnoses (12, 19, 20).

We have previously compared a short (8 days) inpatient rehabilitation program to group-based outpatient ACT (O-ACT) for patients sick-listed due to musculoskeletal or common mental health disorders. We found no significant differences in SA between this short inpatient program and 6 weeks of O-ACT during one year of follow-up (21), and there were negligible differences in self-reported health outcomes (22). However, in Norway, 3-4 weeks of inpatient multimodal occupational rehabilitation (I-MORE) is common for individuals with complex biopsychosocial barriers for return to work. Effects of such programs have never been assessed in a rigorous design.

The aim of this study was to compare the effect on SA of 3.5 weeks I-MORE to the 6 weekly sessions of O-ACT. We hypothesized that the more comprehensive I-MORE would reduce SA compared to O-ACT.

Method

The Regional Committee for Medical and Health Research Ethics in Central Norway approved this open label parallel randomized clinical trial (No.: 2012/1241), registered in clinicaltrials.gov (No.: NCT01926574), and adhered to the CONSORT statement (23). The study protocol is published elsewhere (24).

Eligibility criteria

Participants aged 18-60 years sick-listed (2-12 months, current sick leave status >50%) due to a musculoskeletal, psychological, or general and unspecified disorder (eg, fatigue) as classified by ICPC-2 (the International Classification of Primary Care, second edition) were included. The exclusion criteria were: (i) alcohol or drug abuse; (ii) serious somatic disease (eg, cancer, unstable heart disease) or mental disorder (eg, high suicidal risk, psychosis, ongoing manic episode); (iii) disorders requiring specialized treatment; (iv) pregnancy; (v) current participation in another treatment or rehabilitation program; (vi) insufficient oral or written Norwegian language skills to participate; (vii) surgery scheduled within the next six months; and (viii) serious problems with functioning in a group setting, as assessed by a multidisciplinary team.

Recruitment of participants

The Norwegian Labor and Welfare Administration identified and randomly invited potential participants from its records. Potential participants were asked to respond to the invitation either in writing or by telephone contact with a project co-worker. The project co-worker excluded individuals that self-reported any of the exclusion criteria. We invited the remaining candidates to outpatient assessment of eligibility consisting of individual appointments with a psychologist, a physiotherapist and a physician. This multidisciplinary team made a joint decision on whether the eligibility criteria were met.

Randomization and blinding

Eligible participants were randomized to either I-MORE or O-ACT. The Unit of Applied Clinical Research (third party) at the Norwegian University of Science and Technology (NTNU) conducted the randomization by a flexibly weighted procedure, which ensured that the rehabilitation center had enough participants to run monthly groups in periods of low recruitment. One of the researchers analyzed the primary outcomes while blinded to allocation. It was not feasible to blind primary researchers in preparation and analysis of the dataset due to knowledge of the unequal group sizes.

Interventions

The I-MORE program was provided at Hysnes rehabilitation center located in a rural setting one-hour travel from St. Olavs hospital in the city of Trondheim, Norway. I-MORE lasted 3.5 weeks and was more comprehensive than O-ACT, which mainly consisted of group-based ACT (2.5 hours/week for 6 weeks) at St. Olavs hospital. The length of the inpatient and outpatient interventions reflected common clinical practice. I-MORE comprised various treatment modalities such as physical exercise, work-related problem solving and a development of a written return-to-work plan in addition to ACT, whereas O-ACT consisted mainly of ACT. Mindfulness was integrated in several elements within both interventions. Details of the two programs are described in table 1 and in the protocol article (24). Adherence to- and competence in ACT was ensured by the same peer reviewed ACT trainer through video supervision and mentoring of the clinicians in both interventions.

Outcome measures

The primary outcome measures were the cumulative number of SA days (total number of whole workdays lost) within 6 and 12 months follow-up (see statistics section for details). Secondarily, time until sustainable return-to-work (4 weeks without SA) was assessed up to 12 months. The SA data are based on medically certified SA, work assessment allowance and changes in permanent disability pension during follow up, obtained from the National Social Security Registry. Employees at the Norwegian Labor and Welfare Service registered and provided SA data. They were blinded to treatment allocation.

Self-reported secondary health outcomes were pain (25), anxiety and depression symptoms (26), subjective health complaints (27) and health-related quality of life (28), all measured as continuous scale scores and described in detail previously (21, 22). The participants answered web-based questionnaires at baseline, at the start and the end of the interventions, and at 3, 6 and 12 months of follow-up.

Sample size

The sample size calculations are described in detail elsewhere (21, 29). An average SA of 60 [standard deviation (SD) 40] and 90 (SD 60) days for I-MORE and O-ACT respectively, would require 61 persons for each group. We aimed to include 80 persons in each arm allowing for 20% attrition or loss to follow-up.

Statistical analysis

The cumulative number of SA days at 6 and 12 months after inclusion were calculated and compared for the two programs using the Mann-Whitney U-test (30). Sickness absence days were calculated according to a 5-day workweek adjusted on a monthly basis for parttime employment, partial sick leave and changes in permanent (partial) disability benefits, enabling a count of cumulative days compensated with benefits (total number of whole workdays lost) (21). We graphically displayed differences by plotting the median number of SA days in each intervention group as a function of time (cumulative median). For time until sustainable return to work, Kaplan Meier curves were estimated and compared using the log rank test (30). Return-to-work hazard ratios were estimated

using the Cox proportional hazard model and the Efron method for ties (31), with and without adjustment for gender, age, education, main diagnosis for sick leave and length of sick leave at inclusion. Time was calculated as the number of months from inclusion, and participants were censored at the first month without SA or at the end of follow-up (12 months). The proportionality hazards assumption was tested using the Schoenfeld Residual test (32). Selfreported health outcomes were analyzed as repeated measurements over time using linear mixed models (33), modelled without random slope (only random intercept) if the full model did not converge. Analyses were performed according to the intention-to-treat principle. Additional per protocol analyses were done by excluding participants that withdrew after randomization (before or during the programs) and/or attended less than 60% of the sessions of O-ACT.

We performed sensitivity analyses with sustainable return to work defined as 2 and 3 months without receiving benefits. We considered $P<0.05$ (two-tailed) to be statistically significant. Precision of the estimates was assessed by 95% confidence intervals (CI). All analyses were done using STATA 13.1 (StataCorp, College Station, TX, USA).

Results

Of 3808 persons invited to take part in the study, 271 accepted the invitation and 166 were randomized to I-MORE (n=86) or O-ACT (n=80). See figure 1 for information about the flow of participants, dropouts and missing data.

Participants' characteristics

The mean age of the participants was 46 (SD 9.5) years and the majority was women (79%). About 60% of the participants did not have education beyond high-school level, and the median length of sick-leave reimbursement during the last 12 calendar months prior to inclusion was 210 calendar days (IQR 170-265). Baseline characteristics for the two intervention groups showed only minor differences (table 2).

Sickness absence and return to work

The I-MORE participants had a median of 85 (IQR 33-149) SA days at 12-month follow-up, significantly less than the O-ACT group with 117 days (IQR 59-189; Mann-Whitney U-test; P=0.034). At 6 months followup, the median number of SA days was 51 (IQR 27-85) for I-MORE and 65 (IQR 42-97) O-ACT, respectively (Mann-Whitney U-test; P=0.114), see figure 2.

In total, 50 of the 86 participants in I-MORE and 31 of the 80 participants in O-ACT achieved sustainable return to work. Figure 3 shows the Kaplan-Meier plot. The difference between the programs was statistically significant (log rank test, P=0.009). The unadjusted return-to-work hazard ratio was 1.9 (95% CI 1.2-3.0), in favor of I-MORE and was unchanged after adjusting for age, gender, level of education, length and cause of sick leave (1.9; 95% CI 1.2-3.2).

The sensitivity analyses defining return to work as 2 and 3 months without receiving benefits showed similar hazard ratios (1.8 and 1.7) as the main analyses.

Per protocol analysis

The median number of SA days during 12 months followup was 90 (IQR 33-170) versus 108 (IQR 58-156) days for I-MORE (N=69) and O-ACT (N=61), respectively (P=0.30). The respective sustainable return-to-work rates were 55% (N=38) and 43% (N=26) and the unadjusted hazard ratio was 1.4 (95% CI 0.85-2.44, P=0.17).

Self-reported health and quality of life

There were no statistically significant differences between the programs in these secondary outcomes during 12 months of follow-up, except for a small difference in average pain in favor of O-ACT (estimated mean difference -0.95, 95% CI -1.7- -0.2 on a 0-10 numeric rating scale). Both groups improved anxiety, depression, and quality of life outcomes during follow up (table 3).

Discussion

As hypothesized, I-MORE reduced SA more than O-ACT, and the time to sustainable return to work was shorter for I-MORE. Self-reported health outcomes (pain, distress and health-related quality of life) were largely similar between the groups during one year of follow up.

Our previous investigation of a shorter (8 days) inpatient program did not reduce SA compared to O-ACT (21). We are not aware of other studies that have examined the effect of a comprehensive inpatient occupational rehabilitation

program comparable to our current study. In Norway, an intensive outpatient program consisting of six hours of daily activities for four weeks showed no overall effect on return to work compared to ordinary treatment in primary care (34). However, the same research group later reported that the individuals with the most complex problems returned to work faster when given the intensive rehabilitation program (35). Also, in a Norwegian study providing work-focused cognitive therapy combined with job support to individuals with common mental disorders, only the sub-group of individuals with the most complex problems and the longest SA benefitted from the intervention, and the effect on increased work participation was sustained after 4 years of follow up (36). Similar to the aforementioned studies (35, 36), the individuals in our study were long-term sickness absent (median 210 days in the preceding year).

Several factors could explain the superiority of I-MORE versus O-ACT impact on SA. As this study did not utilize a factorial design, it is not possible to ascribe the superiority of I-MORE to specific contrasts. The most notable differences between the programs were that I-MORE was inpatient, more intensive and multimodal - incorporating physical exercise and psychoeducational sessions. Living at the rehabilitation center for 3.5 weeks provided a break from daily life and gave more time for contemplation, discussion with peers, and integration of new coping strategies. The regulated schedule and a fixed wake-up time may have provided a frame for improved sleep and better coping with fatigue (37, 38). Psychoeducational sessions alone did not enhance return to work in a Danish study (39), but in synergy with other components of an inpatient multimodal intervention it might have contributed positively. We previously reported that a sub-sample of participants in I-MORE improved their cardiorespiratory fitness during the program, and increased further after a year (40). Still, we found little support that differences in self-reported health outcomes (table 3), or changes in expectancies about return to work (41), could explain the differences in SA between programs. This is in line with other studies observing that returning to work and improving health outcomes are not necessarily concurrent events (42, 43). Moreover, participants in O-ACT did not create a return-to-work plan, but an action plan in accordance with their most important values. This may also explain why I-MORE improved work outcomes compared with O-ACT.

Workplace involvement is considered a critical factor in effective return to work programs (6), but our results suggest that I-MORE interventions can be successful without this component. Another study from our group provided no evidence that adding a workplace intervention could further improve work participation outcomes (44). Finally, also considering our previous negative findings of a shorter inpatient program (21), our results support the current practice in Norway of 3-4 weeks of inpatient occupational rehabilitation.

A particular strength of this randomized study is the use of high-quality sick leave registry data, which assured complete data regarding SA and return to work. In contrast, less than half of the participants answered the questionnaires at the 12-month follow-up. Assuming missing at random, the mixed-model approach alleviates this problem by applying likelihood-based analyses using all available data (33). The number of missing questionnaires were fairly similar for the two groups at 6 and 12 months, but we cannot disregard the possibility of an attrition bias for the secondary outcomes. Blinding of participants and caregivers regarding allocation was not feasible. Primary researchers were not blinded in preparation of the dataset. However, one of the authors were blinded to allocation and performed a separate analysis of the primary outcome measures before commencing with further analyses and discussing the findings. Moreover, the employees at the Norwegian Labor and Welfare Service that prospectively register SA data were unaware of group allocation. Another particular strength of the study design was that the Norwegian Labor and Welfare Service invited participants among those fitting the eligibility criteria in the registry, eliminating referral bias and potentially increasing the external validity of the results. However, only 38% (of 3808 invited) responded, and only 271 underwent a full clinical multidisciplinary eligibility assessment (figure 1). Since we do not know how many of those not responding that would have fulfilled the eligibility criteria, we cannot rule out a "self-selection" bias, possibly limiting the generalizability of the results to situations with similar recruitment methods. Another issue is that participants had to be willing to leave their home for 3.5 weeks to participate in I-MORE. Moreover, the differences in SA diminished in the per protocol analysis. This could be explained by the different patterns of withdrawal in I-MORE (before start) and O-ACT (during the intervention). It is conceivable that individuals

that were able to return to work when the intervention started, would opt for this rather than 3.5 weeks of inpatient rehabilitation. Conversely, weekly O-ACT could be combined with work, making it unnecessary to withdraw before the program started. In addition, individuals who were unable to participate once a week were probably those least able to work. A limitation of our study is that we have no information on how O-ACT would have compared to usual care. Another limitation is that no scoring of therapists' adherence to or competence in ACT was done. However, the same peer-reviewed ACT trainer supervised clinicians in both interventions. In addition, a focus group interview study showed that all the relevant ACT processes of behavioral change were reflected in the I-MORE participants' experiences (20).

Finally, since legislation, social security systems and occupational rehabilitation services differ extensively between countries; one should consider contextual factors before implementing this intervention, especially in parts of the world other than the Nordic countries.

Concluding remarks

Among individuals on long-term SA due to musculoskeletal or common mental health disorders, I-MORE over 3.5 weeks reduced SA compared with 6 weekly sessions of O-ACT in the year after inclusion. Studies with longer follow-up and economic evaluations should be performed.

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The authors declare no conflicts of interest.

Sidebar

Three to four weeks of inpatient occupational rehabilitation is mainstream in Scandinavia, but the effects have not been investigated. This is the first study to show that, among individuals on long-term sickness absence due to musculoskeletal- or common mental disorders, 3.5 weeks of inpatient multimodal occupational rehabilitation significantly reduced sickness absence compared with 6 weekly sessions of outpatient acceptance and commitment therapy.

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DETAILS

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The effect of training for a participatory ergonomic intervention on physical exertion and musculoskeletal pain among childcare workers (the TOY project) – a wait-list cluster-randomized controlled trial

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ABSTRACT (ENGLISH)

Objective Many employees have high physical exertion at work and suffer from musculoskeletal pain (MSP) leading to sickness absence with large costs. Participatory ergonomics is a potentially effective intervention for reducing physical exertion, MSP and sickness absence. The main aim of this study was to investigate the effectiveness of a 20-week workplace participatory ergonomic intervention among childcare workers on physical exertion and MSP. Methods In a two-arm cluster-randomized trial, 190 workers were recruited from 16 childcare institutions and randomly assigned to either a 20-week participatory ergonomics intervention consisting of three training workshops or a control group receiving usual care. Primary outcomes were physical exertion during work, maximal pain intensity, number of pain regions, and pain-related work interference. Secondary outcomes were MSPrelated sickness absence, need for recovery (NFR), employee involvement, and self-efficacy. We followed the intention-to-treat principle and adhered to the registered study protocol (ISRCTN10928313). Results After 20 weeks, half the workers noticed some positive changes in their work. However, there were no statistically discernible effects in physical exertion, maximum pain intensity, pain-related work interference, or number of pain regions. We found a significant reduction of MSP-related sickness absence in the intervention compared to the control group [-0.48 days per month (95% confidence interval (CI), -0.8- -0.1]. We found no significant effects in NRF or involvement of employees, but self-efficacy was reduced in the intervention compared to the control group [-0.2 (95% CI, -0.3- -0.0)]. Conclusion This 20-week training for a participatory ergonomic intervention in childcare workers did not show effects on physical exertion and MSP, but was both feasible and effective in reducing MSP-related sickness absence.

FULL TEXT

Headnote

Objective Many employees have high physical exertion at work and suffer from musculoskeletal pain (MSP) leading to sickness absence with large costs. Participatory ergonomics is a potentially effective intervention for reducing physical exertion, MSP and sickness absence. The main aim of this study was to investigate the effectiveness of a 20-week workplace participatory ergonomic intervention among childcare workers on physical exertion and MSP. Methods In a two-arm cluster-randomized trial, 190 workers were recruited from 16 childcare institutions and randomly assigned to either a 20-week participatory ergonomics intervention consisting of three training workshops or a control group receiving usual care. Primary outcomes were physical exertion during work, maximal pain intensity, number of pain regions, and pain-related work interference. Secondary outcomes were MSPrelated sickness absence, need for recovery (NFR), employee involvement, and self-efficacy. We followed the intention-to-treat principle and adhered to the registered study protocol (ISRCTN10928313).
Results After 20 weeks, half the workers noticed some positive changes in their work. However, there were no statistically discernible effects in physical exertion, maximum pain intensity, pain-related work interference, or number of pain regions. We found a significant reduction of MSP-related sickness absence in the intervention

compared to the control group [-0.48 days per month (95% confidence interval (CI), -0.8- -0.1]. We found no significant effects in NRF or involvement of employees, but self-efficacy was reduced in the intervention compared to the control group [-0.2 (95% CI, -0.3- -0.0)].
Conclusion This 20-week training for a participatory ergonomic intervention in childcare workers did not show effects on physical exertion and MSP, but was both feasible and effective in reducing MSP-related sickness absence.
Key terms MSD; musculoskeletal disease; musculoskeletal disorder; RCT; sickness absence; workplace intervention.
Key terms: childcare; childcare worker; cluster-randomized controlled trial; ergonomic; ergonomic intervention; intervention; MSD; musculoskeletal; musculoskeletal disease; musculoskeletal disorder; musculoskeletal pain; physical exertion; randomized controlled trial; RCT; sickness absence; sickness absence; TOY project; training; wait-list; workplace intervention
There are more than 671 million children under five years of age in the world today. Given that labor force participation rates exceed 60% globally, a large number of these children need some sort of non-parental care during the day (1). In particular womens' labor force participation is highly depended on availability of high quality childcare (2). Thus, there is a great need for healthy and fit childcare workers. However, childcare workers generally appear to suffer from poor health (3, 4). Danish childcare workers report a high prevalence of musculoskeletal pain (MSP) and sickness absence (5). Preventive initiatives to improve health are, therefore, important for this occupational group (6). The workplace holds great potential for addressing these health issues and promoting longer working lives.

MSP is a main contributor to sickness absence (7), and work-related factors are among the most important intervention targets to prevent MSP and MSP-related sickness absence (8). These factors particularly involve high physical workload [eg, physical exertion (8, 9)], which has been found to be prevalent among childcare workers (5, 10, 11). The physical demands of working in childcare include the need to lift, carry, and support children in a range of activities, requiring several demanding body postures and movements, such as bending forward and twisting of the back and sitting on the floor (10). However, childcare work can also be mentally and emotionally exhausting and stressful for some individuals (12). Another important factor in those exposed to high physical work demands is the need for recovery (NFR) after a workday, which is greatest among workers who experience high levels of time pressure and physical work demands (13). Moreover, high NFR after work is associated with MSP (14) and increases the risk of subsequent sickness absence (15). Thus, there is a need for effective and feasible interventions to reduce high physical exertion during work and NFR after work, thereby preventing MSP and reducing sickness absence due to MSP among childcare workers.

Participatory ergonomics programs are commonly used as workplace interventions for prevention of MSP (16, 17). The involvement of workers in the process is essential as it ensures that participants take responsibility for and ownership of risk identification, solution development, and implementation of change (18), all of which is important for intervention effectiveness (19, 20). The participatory ergonomics process encourages workers to be involved in optimizing their own work routines, consequently decreasing work-related risk factors (21) and thereby improving their health (22). However, evidence on the effectiveness of participatory ergonomics for reducing physical exertion, MSP, NFR and MSP-related sickness absence is incomplete (16, 23-25).

Our aim of study was to investigate the effectiveness of a participatory ergonomic intervention at the workplace over 20 weeks in childcare workers on the primary outcomes physical exertion and MSP and the secondary outcomes MSP-related sickness absence, NFR, employee involvement, and self-efficacy. We hypothesized that the implementation of the 20-week participatory ergonomic intervention would reduce physical exertion and MSP among childcare workers compared to usual practice (26).

Methods

Between August 2017 and July 2018, we conducted a two-arm, cluster-randomized controlled study with a waiting-list control. Clusters were formed based on childcare institutions and randomly assigned to two different arms (immediate versus delayed intervention, 20 weeks apart). This design yielded the possibility to offer the intervention

to the control group after the intervention had been implemented in the intervention group, thereby decreasing the risk of hampering implementation due to logistical issues and reduced organizational commitment (27, 28). We published a study protocol prior to enrolling participants (26). The trial was prospectively registered (ISRCTN10928313). The Danish National Committee on Biomedical Research Ethics (ie, the local ethics committee of Frederiksberg and Copenhagen) has evaluated a description of the study and concluded that, according to Danish law as defined in Committee Act 2 and 1, the intervention described need not be reported to the local ethics committee (Ref number: 16048606). We obtained written, informed consent from all participants before they enrolled in the trial.

Participants

Details regarding the recruitment procedures of workplaces (childcare institutions) and workers have been reported elsewhere (26). In short, the childcare institutions were recruited with assistance from the municipality of Copenhagen after presenting the project at a meeting of region managers. Eligibility criteria for participation in the study for the institutions were: (i) childcare for children aged 0-3 years, (ii) >9 employees (childcare workers), and (iii) no recent (within the previous year) participation in an ergonomics course from the Work Environment Consultancy of Copenhagen. There were 29 eligible institutions in total, and all their childcare workers were eligible for participation. Since this was an organizational intervention, all childcare workers were expected to participate. Due to the design of the intervention, we only included those workers who we suspected would be at the workplace during the intervention period, meaning that if we knew that a worker would end her/his employment during the study period, he/she was not included in our study sample for the trial (ie, the evaluation) but could still participate in the activities at work.

Randomization and blinding

For practical reasons, the baseline measurement took place after randomization but before any intervention treatment. This was done because the workplaces needed to plan the workshops that were carried out as part of the intervention in advance. All childcare institutions (clusters) gave initial agreement to participate before we performed the randomization. Since the intervention was group-based, and to avoid contamination between workers, the randomization was performed across clusters at the childcare institution level balanced on size. The study was dimensioned to enroll approximately 200 workers. An independent data manager performed the randomization by using a computer-generated randomization using the SAS statistical software for Windows 9.4 (SAS Institute, Cary, NC, USA) developed by an independent statistician. Blinding of participants was not possible due to the nature of the intervention. However, data collection was performed using text messages and all persons collecting/handling data were blinded to group allocation.

Procedures

All childcare workers in the intervention group were involved in the participatory ergonomics process. Ergonomic consultants from the Work Environment Consultancy of Copenhagen (occupational therapists and physiotherapists) guided the process. The participatory ergonomic process followed 6 steps: (i) identification of risk factors, (ii) analysis of risk factors, (iii) solution building, (iv) prototype implementation, (v) prototype evaluation, and (vi) solution adoption. A main feature of this participatory ergonomics intervention was the integration with the core work tasks as previously recommended for improving implementation (6, 29). The first workshop lasted 3 hours and was conducted in week 2. The two follow-up meetings lasted 1.5 hours each, the first meeting was conducted approximately six weeks after the first workshop and the final meeting was conducted approximately four weeks after the second meeting. In addition, each workplace was offered one ergonomic consultant visit. We observed a selection of workshops and assessed the content against prespecified criteria to check the workshop content was as intended (fidelity). Those in the control group followed usual practice from baseline to 20-week follow-up. This group received the intervention after the 20-week follow-up. More information about the intervention can be found in the study protocol (26).

Outcomes and measurements

Data were collected at 4, 8, 12, 16, and 20 weeks after randomization by use of electronic questionnaires sent via

text message to participants' mobile phone (a link to a questionnaire in survey exact). The two primary outcomes of this study were self-rated physical exertion measured on a 0-10 Likert scale (30) and MSP, measured as: (i) maximal pain intensity [0-10 on a numeric rating scale (NRS)] in any one of eight body regions (low back, neck, shoulders, knees, elbows, hands, hips, feet/ankles), (ii) number of pain regions (calculated as number of pain regions with an episode of pain (defined as >1 day with pain in a body region and with an intensity of >3 on the NRS), and (iii) pain-related work interference (days in the previous four weeks with pain that limits ability to do the work). Secondary outcomes were: (i) self-reported sickness absence due to MSP (days) (31) measured by questionnaire every four weeks from baseline to week 20; (ii) self-efficacy (32) measured by questionnaire at baseline and at week 20; (iii) NFR (33, 34) measured by questionnaire at baseline and at week 20; and (iv) employee involvement (35) measured by questionnaire at baseline and at week 20.

Process measures - changes in work

At week 20, the intervention group was asked to score statements about changes in work adapted from Nielsen &Randall's framework (36) about implementation, which was developed specifically for organizational level occupational health interventions. The statements posed were: (i) Through the implementation of the intervention, we finally get to straighten up some bad work methods that we had accepted; and (ii) New procedures have been introduced after the implementation of the intervention. The answer categories were on a 5-point Likert-type scale, from strongly disagree to strongly agree.

Statistical analyses

A sample of 192 participants (96 per group) corresponding to approximately 16 clusters in total was required to ensure 80% power to statistically demonstrate a relevant effect in physical exertion of 1 point (20). We estimated the effect of the intervention on the primary outcome using a mixed model for repeated measures. We treated time as a categorical variable (week 4, 8, 12, 16, and 20) and included group ·time interactions to determine treatment effects at each time point. In addition, we took into account the possible differences between the groups at baseline. For this, a model was developed in which the treatment variable was not part of the model, but its interaction with time was (37). We set statistical significance at $P<0.05$ for a 2-sided test. The primary analysis was by intention-to-treat, including all eligible randomized participants who provided follow-up data. We compared demographic characteristics between dropouts and completers.

Results

Figure 1 shows the flowchart of the trial. Of 222 eligible workers from 16 workplaces, 190 (86%) wanted to participate and provided baseline data; 32 were excluded for lack of data. In total, 96 and 94 childcare workers were randomized to the intervention and control groups, respectively. After the 20-week intervention period, there were 19 (20%) and 16 (17%) workers lost to follow-up in the intervention and control groups, respectively. Table 1 shows baseline characteristics of the workers in both groups. There was a slight difference between the two groups with respect to gender. However, other demographic variables were similar. For both the primary and secondary outcomes there were some differences between the groups at baseline. We controlled for this difference in the statistical analysis by including baseline data of the respective variables in the model.

There were small differences in baseline characteristics between dropouts and completers. Dropouts were younger than the completers (28 versus 39 years). On other baseline characteristics the two groups were similar (data not shown).

Process measures

Dose delivered and dose received. The intervention was delivered by three ergonomic consultants from the Work Environment Consultancy of Copenhagen. All planned activities were delivered (table 2). In total, 88%, 70% and 62% of the workers participated in the first, second and third workshops, respectively. In addition, 43 (45%) of the workers participated in all three workshops, 32 (33%) participated in two workshops, 17 (18%) participated in only one workshop, while four (4%) did not participate in any of the workshops (data not shown). The reasons for not participating in the workshops were employment ceased, vacation, leave, sickness absence or other/unknown.

Appraisal of intervention. Most participants were satisfied with the intervention (78%) and found it relevant (82%). In

addition, nearly all (92%) of the participants considered the intervention to be relevant for other childcare institutions (data not shown).

Changes in work. After implementation of the intervention, 58% of the participants agreed they had finally addressed some bad work methods they had previously accepted, and 50% agreed that new procedures had been introduced.

Intervention effects. Table 3 shows the intervention effects. At week 20, there were no statistically significant effects in physical exertion, maximum pain intensity, pain-related work interference, or number of pain regions. However, the estimates in mean treatment effect between groups at week 20 showed a small reduction in physical exertion and maximum pain intensity in the intervention group.

We found statistically significant effects in the intervention group on reduction of sickness absence due to MSP at week 20 compared to the control group. This corresponded to an intervention effect after 20 weeks for sickness absence due to MSP of -0.4 days per month [95% confidence interval (CI), -0.8- -0.1].

At week 20, there were no significant effects in NFR or involvement of employees. However, there was a statistically significant reduction in self-efficacy of -0.2 (95% CI, -0.3- -0.0) in the intervention compared to control group.

Discussion

We hypothesized that the implementation of the 20-week participatory ergonomic intervention would reduce physical exertion and MSP among childcare workers compared to usual practice. This hypothesis was not confirmed. Nevertheless, the participatory ergonomic intervention was both feasible and effective in reducing MSP-related sickness absence.

Our findings contrast with a systematic review concluding that participatory ergonomics was effective in reducing MSP (16). However, the results obtained from our study are in accordance with other randomized controlled trials, reporting that participatory ergonomics was not effective in reducing MSP (24, 38).

By introducing participatory ergonomics, we aimed to minimize risk factors for MSP at work and improve the work tasks perceived as physically demanding. After the intervention, no significant effect was found for physical exertion or MSP when comparing the intervention with the control groups. In addition to these findings, we did not find any significant effects on NFR. According to our program logic, due to the participatory nature of the intervention, we expected the intervention to have an effect on self-efficacy and employee involvement (26). However, this was not the case. On the contrary, we found a small reduction of 0.15 on a scale from 0-4 in self-efficacy in the intervention group. It is hard to interpret if this change is an intervention effect or just a chance finding. Furthermore, we question whether such a small reduction is of any practical relevance.

When an intervention does not show an effect on the primary outcomes, it is important to consider whether this is a theory or implementation failure (29, 39, 40). With respect to implementation, all intervention workshops were successfully delivered. However, the dose received decreased over time, resulting in only 62% of the participants participating in the last workshop. This number, however, is comparable to other participatory ergonomics interventions (41). In addition, the measures regarding changes in work showed that 50-58% of the participants said the intervention resulted in changes in their work. This number might point towards implementation failure, since only half of the childcare workers said that changes had been made. In general, many ergonomic intervention studies lack information about implementation (17, 42). In our study, we have also gathered information about specific work exposures by objective measurements. However, there is a need for a deeper investigation of specific exposures related to the intervention. This is out of the scope of this paper but will be reported in a separate paper (26).

With respect to theory failure, one reason may be related to difficulties in evaluating participatory interventions. Due to the participatory approach, we do not know much about the actual content of a participatory ergonomic intervention, eg, risk identification or solution development, which then becomes a black box (43). Therefore it is important to consider whether the chosen outcomes are the most optimal for evaluating the effectiveness of participatory ergonomics interventions.

The participatory ergonomic intervention was effective in reducing MSP-related sickness absence. This finding is in accordance with another study among employees in pre-schools from Denmark investigating a participatory

organizational level intervention with a focus on the core task at work (6). A main feature of our participatory ergonomics intervention was also the integration with the core work tasks. This was, in particular, how to make the children more independent of active assistance from the childcare workers (eg, climbing up in the crib and changing table, getting outdoor clothes on) so that the physical work demands could be decreased among the childcare workers. The intervention effect on MSP-related sickness absence could therefore be explained by the children requiring less assistance, possibly making the childcare worker better able to work with the same level of MSP. The reduction in MSP-related sickness absence after 20 weeks was very high (corresponded to a reduction of 88% from baseline to follow-up) and thus of substantial importance for the workplace. However, we do not know whether it was the focus on the core tasks at work that resulted in the reduced MSP-related sickness absence or if other mechanisms were at work. This should be investigated by further analyses of the process evaluation data from the study.

Another main finding of the study was the high feasibility of implementing the participatory ergonomic intervention in terms of high delivery of the intervention and the moderate dose received. This is possibly also related to the focus on the core work tasks, making the intervention more relevant for the childcare workers, and not considering sideline activities with limited relevance (29). This was also seen in the positive appraisal of the intervention with nearly all (92%) of the participants considering the intervention to be relevant for other childcare institutions

Strengths and limitations of the study

The cluster-randomized controlled trial design is a methodological strength since it minimized the risk of contamination between the intervention and reference group and reduced the risk for bias. Repeated measurements with short recall were used to measure study outcomes and we used measures that have all been found to have a reliable validity (30, 31). Another strength is that consultants delivered the intervention and were not involved in the evaluation. Lastly, this study was executed in real working-life settings, which makes it easier to generalize the effects to similar workplaces.

A limitation of this study is the loss to follow-up rates on the primary and secondary outcomes found after 20 weeks. Unfortunately, loss to follow-up is a common problem among prevention studies (44). Checking our data for selective dropout revealed that dropouts did not differ from completers. Also, since this is an organizational intervention, it did not focus on individual workers. Thus, individual randomization was not feasible. Moreover, due to the interventional trial design, participants were not blinded to group allocation. Finally a limitation is that we did not measure changes in work very well.

Concluding remarks

A 20-week workplace participatory ergonomic intervention in childcare workers did not show effects on the primary outcomes of physical exertion and MSP, but was both feasible and effective in reducing MSP-related sickness absence.

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Sidebar

Surprisingly little research has been conducted on childcare work. This study contributes to closing the research gap of lack of research for this occupational group. The 20-week workplace participatory ergonomic intervention among childcare workers was both feasible and effective in reducing musculoskeletal pain-related sickness absence and is thereby beneficial for society.

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Risk of being granted disability pension among incident cancer patients before and after a structural

pension reform: A Danish population-based, matched cohort study

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ABSTRACT (ENGLISH)

Objective This study aimed to examine the risk of being granted a disability pension (DP) among incident cancer patients up to five years after diagnosis compared to a match control group, before and after the structural reform of the Danish Disability Pension Act in 2013. Methods All 20-60-year-old incident cancer-diagnosed individuals from 2000 to 2015 were identified in the Danish Cancer Registry. A control group, not previously diagnosed with cancer, was identified in Statistics Denmark matched by gender, age, education, and household income. Risk differences (RD) in cumulative incidence proportions of being granted a DP between cancer patients and controls were analyzed before and after the reform. Results In total, 111 773 incident cancer patients and 506 904 controls were included in the study. Before reform 10 561 cancer patients and 11 231 controls were granted DP; and 2570 cancer patients and 2646 controls were granted DP after the reform. The adjusted RD of being granted DP was significantly higher for cancer patients versus controls at all time points before the reform. The RD increased the most during the first (RD 3.6, 95% CI 3.5-3.7) and second (RD 7.2, 95% CI 7.0-7.4) follow-up year and levelled off the remaining three years. After the reform, the adjusted RD were lower for all 1-5 follow-up years compared to before the reform (RD range 2.8-7.7, 95% CI 2.6-8.1). Conclusion The 2013 reform of the Disability Pension Act reduced the risk of cancer patients being granted DP. The impact on a personal level should be further explored.

FULL TEXT

Headnote

Objective This study aimed to examine the risk of being granted a disability pension (DP) among incident cancer patients up to five years after diagnosis compared to a match control group, before and after the structural reform of the Danish Disability Pension Act in 2013.

Methods All 20-60-year-old incident cancer-diagnosed individuals from 2000 to 2015 were identified in the Danish Cancer Registry. A control group, not previously diagnosed with cancer, was identified in Statistics Denmark matched by gender, age, education, and household income. Risk differences (RD) in cumulative incidence proportions of being granted a DP between cancer patients and controls were analyzed before and after the reform.

Results In total, 111 773 incident cancer patients and 506 904 controls were included in the study. Before reform 10 561 cancer patients and 11 231 controls were granted DP; and 2570 cancer patients and 2646 controls were granted DP after the reform. The adjusted RD of being granted DP was significantly higher for cancer patients versus controls at all time points before the reform. The RD increased the most during the first (RD 3.6, 95% CI 3.5-3.7) and second (RD 7.2, 95% CI 7.0-7.4) follow-up year and levelled off the remaining three years. After the reform, the adjusted RD were lower for all 1-5 follow-up years compared to before the reform (RD range 2.8-7.7, 95% CI 2.6-8.1).

Conclusion The 2013 reform of the Disability Pension Act reduced the risk of cancer patients being granted DP. The impact on a personal level should be further explored.

Key terms Denmark; Disability Pension Act; quality of life; return to work; vocational rehabilitation.

Key terms: cancer; cohort study; Denmark; disability; disability pension; pension; pension reform; quality of life; return to work; vocational rehabilitation

In the Nordic countries, 37% of all patients diagnosed with cancer are of working age, ie, 2-64 years (1). The possibility to engage in paid work is in general an important contributor to quality of life also for the increased

prevalence of working-age cancer survivors as it restores identity and feelings of normality and solves financial concerns (2, 3). Hence, the motivation to return to work is high (4) and reflected in an average of 60% (range 24-94%) of all cancer survivors actually returning to work (5). However, the lower range of return-to-work (RTW) successes implies that cancer survivors may face complications and disabilities that call for vocational rehabilitation (6).

Between 1980 and 2001, the risk of early retirement pension was 55-60% higher among Danish cancer patients compared to a matched control group (7). Since then, the focus on vocational rehabilitation for this group has grown both nationally (8, 9) and internationally (10).

In the framework presented by Labriola (11), legislation is illustrated as a structural factor that overall tries to support individuals in their attempt to recover and return to work. In the Nordic welfare model, a generous benefit system offers financial security to sickness absentees who are unable to work. In cases of permanent work disability that inhibits work attendance, pensions are available. However, life courses have changed in the last century, moving toward a shorter work career due to more time spent on education before entering the workforce and an earlier retirement age. Compounded by the demographic development towards aging populations, countries can no longer afford their current social benefit schemes and must introduce reforms that increase retirement age and facilitate an inclusive labor market allowing people with <100% work ability to participate (12). It is expected that the prevalence of chronic diseases will increase within an aging and inclusive workforce, which may in turn increase sick leave levels and lower productivity (13). In Austria, the retirement age was postponed by approximately two and three years for men and women, respectively (14), which in fact increased employment. However, spillover effects were seen especially in an increase in unemployment benefits, although disability insurance claims were largely unaffected. In Sweden, a social insurance reform was introduced in 2008 that decreased entitlement to sickness benefits and disability pension (DP) (15). Overall, a reduced number of individuals were granted sickness benefits and DP in 2011 versus 2004, but more went on statutory and employment pensions. Another Swedish study investigated the 1995-2010 sick leave rate among employees aged >65 years (16). Even though the prevalence of >65year old employees increased within this timeframe, sick leave rates were lower in 2010 than in 1995.

In January 2013, a reform of the Danish Disability Pension Act was introduced that aimed to reduce the number of granted DP, in particular among persons <40 years (17). The background for introducing this reform was an increasing incidence of granted DP especially to young individuals due to mental causes. The ideology behind the reform was to send a clear signal to young adults that they are not being abandoned and forgotten but supported and offered rehabilitation to improve their quality of life and ability to contribute to society. The reform also introduced multidisciplinary rehabilitation teams within each municipality to initiate rehabilitation efforts for these young adults at risk of being marginalized. The impact of this reform for cancer patients has not previously been studied, and to our knowledge no other studies on DP reforms targeted at primarily young adults have been studied.

As presented in the framework by Labriola (11), several factors related to personality trait, health, and the work environment have been identified as risk factors for DP. In the Danish register-based study by Carlsen et al (7), granted DP were more frequently seen among incident lymphomas and prostate and ovary cancers. Moreover, old age (18), unemployment, and long-term sick leave also influence work termination (19, 20). Incident cancer patients are in general more comorbid than the background population (21), which may affect their work ability and thus increase the risk of premature exit from the labor market (22). Ethnic minority groups have a higher cancer incidence and poorer survival rates than the majority group in western developed countries (23). Moreover, work conditions for low income and low-level educational jobs have been hypothesized as an explanation for the social inequality in cancer survivors' permanent withdrawal from the labor market (24).

From the perspective of the dynamics of work disability prevention, it is therefore important to study, when taking other risk factors into account, how a structural reform affected incident cancer patients' labor market prospects. Thus, this study examined the risk of being granted a DP among incident cancer patients up to five years after diagnosis compared with a matched control group, before and after a 2013 structural reform of the Danish Disability Pension Act.

Methods

Study population

All incident first-time cancer-diagnosed individuals aged 20-60 years in the period January 2000 to December 2015 were identified in the Danish Cancer Registry (CAR) (25) along with date of diagnosis. Since 1943, all incident cancers have been registered in CAR. Only diagnoses categorized according to Nordic cancer statistics (NORDCAN) were included. Thus, non-melanoma skin cancer was excluded as documentation of this condition is considered heterogeneous and incomplete (26).

A control group was identified in Statistics Denmark in 1:5 ratio matched on gender, age (ten-year age strata), highest completed education (primary/high school, vocational education, education <3 years, bachelor degree, and master degree), and household income (< -60 395, -60 394- -20 132, -20 131- -1, 0-20 131, 20 132-40 263, 40 264-60 394, >60 395 euros), defined at the time of diagnosis for the cancer patient. The matched controls had not previously been diagnosed with cancer except for non-melanoma skin cancer.

To ensure that the controls were indeed cancer free, CAR provided the personal identity number to Statistics Denmark of all Danes who, prior to 2000, had a cancer diagnosis. Thus being registered in CAR prior to 2000 prohibited an individual from being eligible as a control.

Matched controls were assigned the same baseline date as the diagnosis date of the cancer patient.

Data sources and procedures

For both the cancer patients and controls, a unique personal identification number assigned to every Danish resident enabled linkage of information from multiple regis- ters: CAR (25), Statistics Denmark, the Danish National Patient Register (DNPR) (27), and the Danish Register for Evaluation of Marginalization (DREAM) (28).

Outcome measures

The cumulative incidence proportion (CIP) of granted DP was measured from baseline and up to a maximum of five years' follow-up. Information about DP was identified in DREAM, which records all social transfer payments on a weekly basis and encompasses information from July 1991 to the present (29). The granting of DP is registered in that particular week where the beneficiary receives the pension and will continue to do so until old age pension, emigration or death occurs. Thus three types of events were treated as competing risks in the analyses.

Data from DREAM has previously been validated against workplace-registered data on sick leave (28, 30) and self-reported information on type of income (28), and both studies found that DREAM provides valid data.

Potential confounders

Ethnicity was identified in DREAM and categorized as Danish, Western (except Danish), and non-Western.

Comorbidity was based on the Charlson Comorbidity Index (CCI) for a period of five years prior to baseline (31-33). The DNPR provided data on 19 selected somatic comorbidities, scored on a 3-point severity scale to create the CCI, which was then categorized as 0, 1-2 and >3.

Long-term sickness absence (>4 weeks) 12-24 months prior to baseline was identified in DREAM and based on weeks with sickness benefits and reported in three categories (0, 1-26 and 27-52 weeks). A 12-month wash out period presiding cancer diagnosis was chosen due to potential confounding from reduced workability one year before the cancer diagnosis (34).

Statistical analyses

The frequencies of matching variables and potential confounders were reported for the cancer and control populations. For descriptive purposes only, the cancer diagnoses were reported and categorized according to NORDCAN [breast, upper-gastro-and-intestines (UPGI), melanoma skin, colorectal, male genitals, lung, gynecological, brain and central nervous system (CNS), blood, kidney and bladder, other] (26).

The CIP of granted DP was counted between baseline and up to 1-5-year follow-up for the cancer and the control groups. Differences in CIP between the cancer and control groups were interpreted as risk differences (RD) and pseudo observations in generalized linear regressions were used for estimation (35, 36).

Entry was defined as the date of cancer diagnosis for the incident cancer patients and their matched controls accordingly. The end of follow-up was defined by the week where DP was granted, the occurrence of competing

risks (old age pension, emigration or death) or end of 1-5-year follow-up, which ever occurred first.
During follow-up in the present study, the Danish Disability Pension Act was reformed in January 2013, by which individuals aged <40 years in principle no longer could be granted a DP. To account for the reform, delayed entry was applied for cancer patients diagnosed before January 2013 and still at risk of being granted DP by January 2013 and onwards. Adjusted for matching variables, crude and adjusted RD were presented.
To assess whether RD significantly changed following the reform, RD were subtracted (after minus before 2013) and 95% confidence intervals (CI) were calculated by the corresponding RD standard errors.
Moreover, 5-year CIP for the cancer population and RD stratified on the matching variables were estimated.
The significance level was set at P<0.05. STATA version 15.1 (StataCorp, College Station, Texas, USA) was used as statistical software.

Ethics

The Danish Data Protection Agency approved this study (1-16-02-445-16). According to Danish law, approval from the Danish National Committee on Biomedical Research Ethics was not needed as this is only provided for projects using biological material or involving biomedical treatment. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (37).

Results

A total of 219 694 20-60-year-old individuals were identified in CAR between 2000 and 2015, and 1 094 399 controls were identified in the matching procedure. Of those, 83 275 (38%) cancer patients were excluded; primarily due to non-cancer diseases (ie, precancerous lesions) and non-melanoma skin cancer diagnosis. That resulted in an exclusion of 412 312 (38%) matched controls. In total, 111 773 incident cancer patients and 506 904 matched controls met the inclusion criteria and were included in the study and followed for up to five years (figure 1).
More 50-60-year-olds were present in the cancer (58.0%) than control (55.8%) population. Also, more cancer patients than controls had primary or high school as their highest achieved education and earned €0-20 131 per year (table 1). More ethnic Danes were diagnosed with cancer than western and non-western residents. Cancer patients had more comorbidity the presiding five years before cancer diagnosis and spend more time on sick leave during the year prior to the wash-out period than the controls. Breast and UPGI cancer were the most incident cancer types, whereas kidney and bladder as well as other cancers had the lowest incidence (table 1).
During the five years follow-up before the reform a total of 10 561 cancer patients were granted DP and 41 718 controls. The adjusted RD of being granted a DP for cancer patients was significantly higher than the controls at all time points (table 2). The RD of granted pensions between the controls and cancer patients were most pronounced within the first and second follow-up year (RD 3.60, 95% CI 3.46-3.74 and RD 7.20, 95% CI 7.01-7.40, respectively) and levelled off the remaining three years.
After the reform, 2570 and 2646 cancer patients and controls were granted DP, respectively. The CIP of being granted a disability pension for cancer patients were lower for all follow-up years than before the reform, ranging from 3.09% (95% CI 2.85-3.33) within the first year to 9.28% (95% CI 8.91-9.66) within the five years follow-up (table 2). The adjusted RDs were statistically significantly smaller after 2013 than before, ranging from RD difference -0.78 (95% CI -1.02- -0.50) to RD difference -2.05 (95% CI -2.51- -1.59) (table 2).
Within the first three follow-up years, the stratified analyses showed a tendency of higher RD between control and cancer men than women granted DP. Within the remaining two follow-up years, this difference levelled off (table 3). After the reform, the difference between men and women remained throughout the five years but at a lower level than before 2013. The younger the age, the smaller the RD observed - both before and after the reform. For those <40 years, the RD were approximately halved after the reform compared to before. For the age groups >39 years, a reduction in RD was seen after the reform but less pronounced than for those <40 years. For the 50-60-year-old group, the RD remained the same after the reform from the second until the fifth follow-up year up (table 3). The reform seemed to reduce the difference in RD for those with the highest achieved educational level and annual income. Whereas for the loweducated and small-income groups, the reduction in RD after the reform were much

smaller than for the more socioeconomically fortunate. For those with a negative yearly income, the tendencies departed somewhat for the low socioeconomical groups and were more comparable with the well-educated and high-income groups.

Focusing solely on the cancer population, the CIP of being granted a DP within the five-year follow-up period were reduced after the reform for all matching variables compared with the CIP before the reform. Unlike the reductions in RD after the reform, the reductions in CIP were not particularly associated with the different levels of the various matching variables. The smallest reduction in CIP (8.98-8.52 = 0.46% points) was observed for the -€20 131- -1 income-strata and the highest was observed for the 40-49-year age-strata (13.26-6.85 = 6.41% points) (table 3).

Discussion

This Danish population-based study compared the CIP of being granted a DP among incident cancer patients up to five years after diagnosis, before and after a structural reform of the Danish Disability Pension Act in January 2013. Overall, we found the RD between controls and cancer patients of being granted a DP were reduced after 2013. This was especially the case for socioeconomically fortunate groups. For the cancer group, the CIPs were overall reduced after the reform and these reductions were less dependent of socioeconomic variables than among the controls.

Labriola's Dynamic Work Disability Model (11) proposed different factors that may affect pathways leading to RTW or termination of work, representing the two possible extremes in the model. Structural factors such as legislation are illustrated as a RTW-promoting mechanism (11). The overall purpose of the 2013 structural reform of the Disability Pension Act was to reduce the number of granted DP in particular among 18-40-yearolds (17). As our findings showed an overall reduced risk of being granted DP among cancer patients after (versus before) 2013, municipal social workers responsible for the granting of DP seem to have translated the legislation according to the intension of the reform, ie, in favor of vocational rehabilitation. However, as the risks were reduced irrespective of gender, age, education and income among the cancer patients within the five-year follow-up, it may point toward a generally decreased disability among cancer survivors and thereby a reduced need for permanent withdrawal from the labor market. However, improvements in early diagnosis and treatments are mentioned as factors responsible for reduced mortality rates (38), whereas the increased prevalence of cancer survivors may experience increased levels of comorbidity, physical, and mental late effects that may reduce work ability (39). Looking at the reductions in RD from before to after 2013, the results pointed in different directions. On one hand, cancer patients were still more likely to be granted DP than controls but, on the other hand, this had also to do with increased risks of DP among the controls depending on their socioeconomic status. The introduction of municipal rehabilitation teams has put emphasis on vocational rehabilitation in general; social workers may be more aware of offering other public benefits than DP targeted to sustain work ability and employability. This is in line with experiences gained from the introduction of social reforms in other countries, where spill-over effects were observed such as increased unemployment rates when retirement age was postponed (14) and an increase of statutory pensions were seen when the entitlement to DP and sickness benefits was reduced (15). It may be an indication of a fulfillment of the reform's overall purpose, namely to increase attachment to the labor market, and thus supporting the assumptions put forward in Labriola's conceptual framework (11). It is, however, important to further investigate if the reform merely maintains individuals on social benefits, other than DP, with no work prospects. From 2013 until the present, an increased CIP of granted DP has been observed in Denmark. This may be a delayed effect of initiated rehabilitation efforts that ultimately did not reveal any work ability (38-40).

Along with the reform, regulations of the employment scheme for partly work-disabled (flexi-job) were also carried out. Special vocational rehabilitation teams within the municipal social services were formed to ensure early interdisciplinary input and support the workdisabled to return to work in ordinary or modified jobs, thus avoiding DP. However, a reduction in granted pensions does not inform about how the work-disabled in general, and cancer patients in particular, experience these new initiatives and whether work participation has indeed increased. Therefore knowledge is needed about those work-disabled who, before 2013, would have been granted a DP but currently are offered alternative means of economic and rehabilitative support. Studies should look into this

potentially vulnerable group of individuals. A cancer diagnosis often leads to new perspectives on life. For some, a re-evaluation of work life (41) may lead to a desire to change occupation or engage in activities such as volunteer work and thus, in some cases, renounce the right to social benefits (including DP). The patientcentered perspective should therefore be further explored as to whether the reform gives individuals the opportunity to engage in activities that are perceived as meaningful and improving quality of life.

In the present study, the cancer patients were more likely to receive DP than controls in both time periods. Similar findings were identified in Carlsen et al's Danish register-based study from 2008 (7), in which an increased risk of 60% and 55% in female and male cancer patients, respectively, was reported compared with matched controls. In Carlsen et al's and the present study, adjustments for known risk factors related to the workplace environment were not possible due to the register-based design. The workplace arena is considered an important stakeholder in vocational rehabilitation (42). Within Labriola's Dynamic Work Disability Model (11), management quality was identified as a possible modifying factor between person-related factors and the pathways between RTW and work termination. This was further substantiated in Feuerstein et al's review (43) where work environment factors were also found to be important in RTW studies among cancer survivors. Along with the introduction of social reforms, it is clear that the involvement of the workplace arena is a requisite for RTW (13) as the work environment needs adjustments to sustain work ability among an aging and not 100% fit workforce, in particular in mentally and physically demanding professions. The workplace arena and its effect on cancer patients' risk of DP should be further explored.

Carlsen et al (7) found that the risk of being granted DP increased with 9% and 8% per ageing year among women and men, respectively, compared with controls. We also found that the risks of DP increased with age among the cancer patients. Fortunately, few were diagnosed with cancer before the age of 40 (16.8%), and fewer were granted a DP in these age groups than among those >40 years both before and after 2013 in the present study. Despite these encouraging results, previous studies have reported that young adults with cancer often struggle during and after the RTW process to sustain work participation (44, 45). Young cancer patients typically experience problems with paying attention, forgetting and keeping up with work (45). Thus, even though young adults are able to return to work, they still need support afterwards to sustain their work participation. However, effective interventions to support sustained RTW and prevent permanent work disability in young cancer patients are scarce (45), and future research is warranted.

Methodological considerations

This study has several strengths due to its populationbased design and high-quality registry data from CAR (25), DNPR (27), and DREAM (9, 28), which limited the risk of selection and information bias. However, the design prohibited adjustments for workplace- and health-related factors such as pain, anxiety and depression, which may have led to confounded risk estimates. Furthermore, the DP reform in 2013 restricted the granting of DP to persons <40 years, which we would have liked to adjust for in the analyses. However, our matching procedure used 10-year age strata and thus, exact age at time of diagnosis and the granting of DP was unknown. We were therefore only allowed to perform delayed entry, ie, both the cancer and control groups had survived beyond January 2013 if diagnosed with cancer prior to that time point and had not yet been granted a DP. We suspect this may be the reason for the control group's increased DP risk after January 2013, possibly leading to underestimated RD after that time point.

As social security schemes vary between countries, the transferability of our results may be limited to the Nordic region, which also has a tax-financed benefit system and is considered to offer generous systems compared with most other countries.

Concluding remarks

This Danish population-based study showed that a 2013 structural reform of the Disability Pension Act reduced the risk for cancer patients to be granted a DP. The differences between controls' and cancer patients' risk of being granted a DP were significantly reduced after the reform. However, reductions were more pronounced among the socioeconomically fortunate versus unfortunate. The impact of the reduced number of granted DP on cancer

patients' quality of life is unknown. The patient-centered perspective should therefore be further explored as to whether the reform provides individuals the opportunity to engage in supportive activities and vocational rehabilitation that are perceived as meaningful and improving of quality of life.

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Sidebar

In January 2013, a structural reform of the Disability Pension Act was implemented in Denmark with the purpose of reducing the number of granted disability pensions, in particular among individuals younger than 40 years. The study results confirm that purpose also among cancer patients. The personal implications of the reform among cancer patients are unknown and should be further explored.

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DETAILS

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Shirangi, A., Wright, J., Blair, E. M., McEachan, R. R. C., & Nieuwenhuijsen, M. J. (2020). Occupational chemical exposures in pregnancy and fetal growth: Evidence from the born in bradford study. Scandinavian Journal of Work, Environment & Health, 46(4), 417-428,417A. doi:https://doi.org/10.5271/sjweh.3878

Objectives This prospective birth cohort study evaluated the effect of occupational exposure to endocrine disrupting chemicals (EDC) during pregnancy on inadequate fetal growth as measured by small-for-gestational age (SGA) and inadequate fetal growth measured by percentage of optimal birth weight (POBW). The study also identified the maternal characteristics associated with an increased risk of exposure to EDC. Methods We studied 4142 pregnant women who were in paid employment during pregnancy and participated in a population-based, prospective 2007-2011 birth cohort study, the Born in Bradford Study, with an estimated participation of 80%. Job titles were coded at 26-28 weeks' gestation at a 4-digit level according to 353 unit groups in the 2000 UK Standard Occupational Classification. They were then linked to expert judgment on exposure to each of ten EDC groups as assessed through a job exposure matrix (JEM). We performed generalized estimation equation modelling by a modified Poisson regression to assess the risk of POBW and SGA associated with an increased risk of chemical exposures. Results The frequency of POBW<85 significantly increased for mothers exposed to pesticides adjusted risk ratio (RRadj) 3.72, 95% confidence interval (CI) 1.40-9.91] and phthalates (RRadj 3.71, 95% CI 1.62-8.51). There was a 5-fold increase risk of SGA for mothers exposed to pesticides (RRadj 5.45, 95% CI 1.59-18.62). Veterinary nurses and horticultural trades were most frequently associated with exposure to pesticides while hairdressers, beauticians, and printing machine minders were associated with phthalates. Conclusion Maternal occupational exposure to estimated concentrations of pesticides and phthalates is associated with impaired fetal growth.

Bonde, J. P. (2020). On endocrine disruption at the workplace – how to get from suggestive to conclusive evidence? Scandinavian Journal of Work, Environment & Health, 46(4), 335-338,335A. doi:https://doi.org/10.5271/sjweh.3897

Bonde explores how to get conclusive evidence on endocrine disruption at the workplace. The health consequences of reproductive hazards at the workplace may be grave for the individual and society. Ensuring a working environment that protects reproductive health must be a high priority. With reference to the precautionary principle, it may be tempting to exclude pregnant women from work that may carry the slightest theoretical risk. But this approach may have strong social and economic consequences for the women who thus do not necessarily benefit from the doubt. Many people need to know more. While experimental studies are important for risk assessment, most rely on epidemiology to address real world occupational exposure scenarios. Epidemiological methods and populations are available, but to ensure progress, a provision of resources is needed to refine assessment of occupational exposure to endocrine disrupting chemicals by ambient air and biological measurements.

Lidén, E., Karlsson, B., Torén, K., & Andersson, E. (2020). Metabolic syndrome – a risk factor for all-cause disability pension: A prospective study based on the swedish WOLF cohort. Scandinavian Journal of Work, Environment & Health, 46(4), 402-409,402A. doi:https://doi.org/10.5271/sjweh.3881

Objective The aim was to study the impact of metabolic syndrome on the risk for disability pension among Swedish employees. Methods A working population-based prospective cohort Work, Lipids and Fibrinogen (WOLF) cohort, N=10 803], was linked to national registry records of all-cause disability pension for the period 1992-2013. Occupational health service data included 1992-2009 anthropometric measurements, blood samples, and questionnaires. Metabolic syndrome was defined according to International Diabetes Federation criteria, and risk for any all-cause disability pension was analyzed using Cox proportional hazard regression as hazard ratios (HR) with 95% confidence intervals (CI) adjusted for age, sex and other covariates. Results Of the employees, 17.9% (men 21.5%, women 9.7%) met the criteria for metabolic syndrome. The prevalence of all-cause disability pension was 15.2% in men with metabolic syndrome and 7.5% in men without metabolic syndrome; for women, the corresponding results were 23.2% and 12.7%. After adjustment for sociodemographic factors, health behaviors, work-related factors, diabetes, and obesity, the risk for all-cause disability pension among subjects with metabolic syndrome displayed an HR of 1.37 (95% CI 1.18-1.60). Results were similar for men and women. In a subgroup,

further adjustment for chronic diseases resulted in an HR of 1.32 (95% CI 1.04-1.68). Conclusion This study demonstrates an increased risk for all-cause disability pension, even after adjustment for other risk factors, among Swedish employees with metabolic syndrome compared to those without at baseline.

Garde, A. H., Nabe-Nielsen, K., Jensen, M. A., Kristiansen, J., Sørensen, ,J.K., & Hansen, Å. M. (2020). The effects of the number of consecutive night shifts on sleep duration and quality. Scandinavian Journal of Work, Environment & Health, 46(4), 446-453,446A. doi:https://doi.org/10.5271/sjweh.3885

Objectives The organization of night shift work affects sleep duration and quality. The aim of this study was to investigate the effects of the number of consecutive night shifts on sleep duration and quality among police officers with night shift work as part of their normal schedule. Methods This quasi-experimental, within-subject crossover study included 73 police officers. All participants performed three work schedules: two, four and seven consecutive night shifts followed by the same number of recovery days, ie, day work or days off (2+2, 4+4, and 7+7). Sleep assessed through sleep diaries and actigraphy after all night shifts and recovery days (totaling 26 days) was compared by use of repeated measures analysis. Results Participants experienced shorter sleep duration (with and without naps), more premature awakening, less difficulty falling asleep, and more non-refreshing sleep after night shifts compared with recovery days. Sleep duration and quality did not change with increasing number of consecutive night shifts. Sleep was shorter and of poorer quality after the last night shift in the 2+2 and 4+4 work schedule compared with the second and fourth night shift, respectively, in the 7+7 schedule. Conclusion Sleep duration was reduced after night shift work and did not increase with more consecutive night shifts, which leads to accumulated sleep debt. Sleep duration was shortest and sleep quality was poorest after the last night shift in a series of night shifts.

Rudkjoebing, L. A., Bungum, A. B., Flachs, E. M., Eller, N. H., Borritz, M., Aust, B., . . . Bonde, J. P. (2020). Work-related exposure to violence or threats and risk of mental disorders and symptoms: A systematic review and meta-analysis. Scandinavian Journal of Work, Environment & Health, 46(4), 339-349,339A. doi:https://doi.org/10.5271/sjweh.3877

Objective This review aimed to examine systematically the epidemiological evidence linking work-related exposure to violence and threats thereof with risk of mental disorders and mental ill-health symptoms. Methods We searched PubMed, EMBASE, PsycINFO and Web of Science to identify original studies that provide quantitative risk estimates. The evidence was weighted according to completeness of reporting, potential common method bias, and bias due to differential selection and drop out, selective reporting, and misclassification of exposure and outcome. Results We identified 14 cross-sectional and 10 cohort studies with eligible risk estimates, of which 4 examined depressive disorder and reported an elevated risk among the exposed pooled relative risk (RR) 1.42, 95% confidence interval (CI) 1.31-1.54, I2=0%]. The occurrence of depressive and anxiety symptoms, burnout and psychological distress was examined in 17 studies (pooled RR 2.33, 95% CI 3.17, I2=42%), and 3 studies examined risk of sleep disturbance (pooled RR 1.22, 95% CI 1.09-1.37, I2=0%). In most studies, common method bias and confounding could not be ruled out with confidence and strong heterogeneity in most outcome definitions invalidate the strict interpretation of most pooled risk estimates. Conclusion The reviewed studies consistently indicate associations between workplace violence and mental health problems. However, due to methodological limitations the causal associations (if any) may be stronger or weaker than the ones reported in this study. Prospective studies with independent and validated reporting of exposure and outcome and repeated follow-up with relevant intervals are highly warranted.

Virtanen, M., Lallukka, T., Kivimäki, M., Alexanderson, K., Ervasti, J., & Mittendorfer-Rutz, E. (2020). Neurodevelopmental disorders among young adults and the risk of sickness absence and disability pension: A nationwide register linkage study. Scandinavian Journal of Work, Environment & Health, 46(4), 410-416,410A. doi:https://doi.org/10.5271/sjweh.3888

Objectives Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and learning disabilities (LD) have an early onset and often persist into adulthood, although their relative contribution to incapacity for work is

unclear. We examined this issue among young adults with ADHD, ASD or LD taking into account socioeconomic factors and comorbid mental disorders. Methods Recorded diagnoses between the ages of 10-35 years between 2001 and 2010 were derived from nationwide inpatient and specialized outpatient hospital registers in Sweden. We identified 15 632 individuals with a main diagnosis of ADHD, 8238 with ASD, and 1038 with LD, and the matched control group without recorded mental disorders (N=124 536). The outcome was the number of register-based sickness absence and work disability pension (SA-DP) days during a maximum of three years follow-up. Results Among men, the rate ratio (RR) of SA-DP was 11.17 95% confidence interval (CI) 9.89-12.60] for ADHD, 35.59 (95% CI 30.30-41.81) for ASD, and 9.20 (95% CI 5.76-14.70) for LD, in comparison to those in the reference group. The corresponding risks among women were RR 12.05 (95% CI 10.30-14.09) for ADHD, RR 28.36 (95% CI 22.96-35.02) for ASD, and RR 9.60 (95% CI 5.83-15.81) for LD. The findings were, to a large extent, similar when individuals on DP at baseline were excluded. Comorbid mental disorders further increased the risk of SA-DP. Educational differences were smaller among the patients than in the reference group. Conclusions Early-onset neurodevelopmental disorders, particularly with comorbidity, have a far-reaching impact on adult life in terms of SA and DP.

Skagseth, M., Fimland, M. S., Rise, M. B., Johnsen, R., Borchgrevink, P. C., & Aasdahl, L. (2020). Effectiveness of adding a workplace intervention to an inpatient multimodal occupational rehabilitation program: A randomized clinical trial. Scandinavian Journal of Work, Environment & Health, 46(4), 356-363,356A. doi:https://doi.org/10.5271/sjweh.3873