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MANUSCRIPT TITLE

The effect of work schedule on prospective antidepressant prescriptions in Sweden: A 2-year sex-stratified analysis using national drug registry data

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ABSTRACT

INTRODUCTION

Depression-related mood disorders affect millions of people worldwide and contribute to substantial morbidity and disability, yet little is known about the effects of work scheduling on depression. This study used a large Swedish survey to prospectively examine the effects of work schedule on registry-based antidepressant prescriptions in females and males over a two-year period.

METHODS

The study was based on an approximately representative sample (n=3980 males, 4663 females) of gainfully employed participants in the Swedish Longitudinal Occupational Survey of Health. Sex-stratified and unstratified analyses were conducted using logistic regression. For exposure, 8 categories described work schedule in 2008: “regular days” (3 categories of night work history: none, ≤ 3 years, 4+ years), “night shift work”, “regular shift work (no nights)”, “rostered work (no

nights)", "flexible/non-regulated hours", and "other". For the primary outcome measure, all prescriptions coded N06A according to the Anatomical Therapeutic Chemical System were obtained from the Swedish National Prescribed Drug Register and dichotomized into "any" or "no" prescriptions between 2008 and 2010. Estimates were adjusted for potential sociodemographic, health, and work confounders, and for prior depressive symptoms.

RESULTS

In fully adjusted models, females in "flexible/non-regulated" schedules showed an increased odds ratio for prospective antidepressant prescriptions (OR=2.01, 95% CI=1.08-3.76), while a decreased odds ratio was observed for the unstratified model "regular shift work (no nights)" category (OR=0.61; 95% CI=0.38-0.97).

CONCLUSIONS

This study's findings support a relationship between work schedule and prospective antidepressant prescriptions in the Swedish workforce. Future research should continue to assess sex-stratified relationships, using detailed shift work exposure categories and objective registry data where possible.

Article Summary

Strengths and Limitations

- Two-year longitudinal design
- Based on a large national survey (the Swedish Longitudinal Occupational Survey of Health) with detailed information on workplace, demographic, and social characteristics
- Addresses a number of common methodological limitations in shift work research through its use of detailed exposure assessment, objectively recorded health outcome measures, and sex-stratified analyses
- Other characteristics that have been linked with negative mental health outcomes, such as long weekly working hours, short shift durations, and the presence/characteristics of shift rotations should also be considered in future studies

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INTRODUCTION

An employee's hours of work are a potentially important influence on their mental health. On the one hand, shift work has been linked to increased symptoms of depression and negative mood, compared to regular day work (1–4). On the other, high levels of work time control have often been identified as having positive influence on health outcomes, such as affective wellbeing and perceived stress (5). Identifying modifiable workplace factors related to depressive outcomes could provide a means to reduce the burden of this disease, since depressive disorders are prevalent in western countries (6), and contribute to substantial morbidity and disability worldwide (7,8). However, studies of the association between work schedule and clinically verified mental illness such depression remain scarce.

Shift workers may be at increased risk of developing mental disorders such as depression due to biological and social disturbances that are caused by their work schedules (9,10). Sleep disturbances in shift workers are well documented (11–13); subjectively and objectively measured sleep disturbances are in turn the most widely reported circadian disruptions associated with depression (14). Also, exposure to light-at-night has been linked to mental health effects, both directly and through its suppression of melatonin (15–17). Finally, the social zeitgeber theory postulates that stressful life events may trigger depressive episodes by disrupting social routines (10).

The potentially positive effects of allowing employees control over their work hours has been ascribed to the promotion of a positive balance between effort and recovery, and between work and non-work life (5). However, the flexibility of boundaryless work (i.e. where employees can decide for themselves when and where to work (18)) may have negative consequences (19). When workloads are high and there are ambiguous norms about work hours, there is a risk that

the employee may feel pressured to restructure their personal time to work, resulting in overwork (20). Mixing work and family time may lead to work-life interference. It may also cause difficulties switching off thoughts of work, such that work never stops, thereby increasing stress and impeding recovery (21).

The nature of the associations between work schedule and mental health remain unclear, largely as a result of methodological challenges (22). First, a lack of clear and well defined exposure definitions increase the potential for measurement error and misclassification (23) bias that have been shown to attenuate effect estimates in prior studies of shift work and depression (24). Second, mental health outcomes are often measured through subjective reporting, that is more susceptible to bias compared to objective health outcome data, particularly for mental health outcomes where stigma is a concern (25). Thirdly, sex-stratified analyses are biologically valid and important to conduct yet this is not always done; an important limitation since both work schedule (26) and rates of reported depressive disorders (8) are known to differ across males and females. There is some evidence of differential impacts of shift work on mental health among men and women (27,28) although the evidence is inconsistent across studies. Finally, self-selection of individuals in to and out of jobs with non-standard work hours (the "healthy worker effect") can bias results toward underestimated effects and is particularly problematic when past exposures are not accounted for.

The Swedish Longitudinal Occupational Survey of Health (SLOSH) (29) is a large national survey that collects detailed information on workplace, demographic, and social characteristics, and can be linked to national health registries in Sweden. The present study utilized data from the SLOSH to examine the prospective effect of work schedule (using detailed categories that incorporated consideration of prior night work history) on antidepressant prescription rates (using objective measures obtained via linkage to a national health registry), in females and in males, over a two-year period.

Shift work, especially where it involves night work, could be expected to be associated with higher rates of antidepressant prescription, due to the chronic disruption of circadian rhythms, sleep and social routines. Female shift workers are expected to have higher rates than their male counterparts, due to the double burden of shift working and family responsibilities (30), as well as

possible psychobiological gender differences in the impact of circadian disruption (31). The impact of flexible work hours on antidepressant prescription rates is more difficult to predict. As noted above, while having control over one's work hours is potentially beneficial, it may also lead to overwork. Women who take on the larger part of family responsibilities may have the most to gain from greater flexibility. However, they may also be more at risk of strain, if they use the increased time control to engage in more non-work responsibilities, rather than using it fully recover and reduce strain (32). Thus no predictions are made with respect to the associations between flexible work and antidepressant prescription rates.

METHODS

Study Sample

This study is based on an approximately representative sample of gainfully employed Swedish individuals participating in the Swedish Longitudinal Occupational Survey of Health (SLOSH). The SLOSH is a follow-up of Swedish Work Environment Survey (SWES) participants, a biennial sample of gainfully employed individuals drawn from the Swedish Labor Force Survey.

The baseline study sample was drawn from the n = 9756 participants who were currently working in the 2008 SLOSH survey wave (this wave was chosen since it yielded a relatively large number of respondents, and collected information on history of night work). This sample was limited to respondents who provided valid answers for work schedule (excluded n = 195), who did not work a regular evening schedule due to small numbers in this category (excluded n = 58), who worked between 8 and 70 hours per week (excluded n = 25 reporting fewer than 8 hours per week, n = 12 reporting more than 70 hours per week, and n = 355 with missing data), and who provided valid answers for all other variables included in the models. This produced an analytic sample of n = 8643 respondents in the 2008 SLOSH wave.

The SLOSH was approved by the Stockholm Regional Research Ethics Board. All SLOSH participants gave informed consent to participate in this study by responding to the questionnaires.

Primary exposure and outcome

For the exposure variable, eight categories were used to describe work schedule in 2008: "regular days with no history of night work", "regular days with history of night work ≤ 3 years", "regular days with history of night work ≥ 4 years", "night work (regular, rostered, or rotating)", "regular shift work (no nights)", "rostered work (no nights)", "flexible/non-regulated hours", and "other". Regular shift work involves working a set of invariantly timed shifts that cycle according to fixed sequence. Rostered work also involves invariantly timed shifts, but the sequence is more ad hoc such that the employee has relatively short notice of which shifts they will be working. Flexible / non-regulated hours involves duty-periods that could vary both with respect to the start and finish times, and which days are worked.

For the outcome variable, data on antidepressant medication prescriptions were obtained from the Swedish National Prescribed Drug Register. This register contains information on all prescribed drugs dispensed from Swedish pharmacies since July 2005 (except for those given in hospitals or nursing homes). This data was anonymously linked to survey respondents through registered personal identification numbers. All Drug Register prescriptions coded N06A according to the Anatomical Therapeutic Chemical System (World Health Organization, 2017) were extracted for the analysis. A dichotomous variable ("yes" or "no" was created to describe any antidepressant prescriptions registered between June 17, 2008 and December 31, 2010, representing a period of approximately 2.5 years following the 2008 survey wave.

Analyses

Logistic regression models were used to examine the prospective association between work schedule reported in 2008 and subsequent antidepressant prescriptions. These models were first constructed with all participants included, then stratified by sex. Model estimates were adjusted for the potentially confounding effects of other variables hypothesized as being risk factors for depression and also related to work schedule.

Demographic & social variables: Sex (for unstratified models) was described with two categories: "male" and "female". Age (reported numerically in the SLOSH) was described with three categories: "20-35", "36-50" and "51-70" years. Chronotype was described with three categories:

"Distinctly or somewhat a morning person", "Distinctly or somewhat an evening person" or "Neither". Significant other status was described with two categories: "single" or "married/cohabitating". Education was described with three categories: "Compulsory", "Upper Secondary/Vocational", and "University or Equivalent". The presence of chronic conditions was described with two categories: "None" or "1 or more", based on the questions "Has a doctor told you that you have": "heart disease", "diabetes", "rheumatic disorder", "musculoskeletal disorder", "obstructive pulmonary disease", or "asthma".

Work variables: Employer type was described with three categories: "private company", "government (local, district, or central", and "other (association/non-profit, own business/Farm, other)". Weekly number of hours worked was described with two categories: "between 8 and 31 hours", or "32 hours or more". Demand-control at work was described with four categories: "high demands, low control", "high demands, high control", low demands, high control", and "low demands, low control", while social support at work was described with two categories: "high" and "low". Both of these variables were based on the 17-question Swedish Demand-Control-Support Questionnare (DCSQ) scale (33). The emotional demands at work variable was described with two categories: "seldom or never" and "often or sometimes", based on the question "Does your work put you in emotionally disturbing situations?"

Previous depression and/or previous antidepressant prescriptions: This variable was described with two categories: "yes" and "no". SLOSH respondents were assigned "yes" if they reported depression in the prior SLOSH wave as assessed with the Symptom Checklist-core depression (SCL-CD6) (34), or if they had been prescribed any antidepressant medications (prescriptions coded N06A) in the Swedish National Prescribed Drug Register in the three years prior to the 2008 SLOSH wave (July 1, 2005 to June 17, 2008).

Demographic and work variables, and previous depression and/or previous antidepressant prescriptions, were entered sequentially as covariates to examine how these factors affected the effect estimates.

RESULTS

Table 1 provides a descriptive summary of variables within the study sample (n = 8643). Females

represented 54% of the total sample. The majority of all respondents (n = 6874, or 80%) reported regular daytime work in 2008; of these, n = 1088 (16%) had previously worked nights. For females, n = 3639 (78%) reported regular daytime work in 2008; of these, n = 449 (12%) had previously worked nights. For males, n = 3235 (81%) reported regular daytime work in 2008; of these, n = 639 (20%) had previously worked nights. Registered antidepressant prescription rates in the post-survey period were 11.4% for females versus 5.8% for males. The highest rates of registered antidepressant prescriptions occurred in both females and males reporting "other" work hours. For females, this was followed by "flexible/non-regulated" hours and "roster work, days and evenings only". For males, this was followed by "regular days (4+ years of night work history)" and "regular days (3 years or less of night work history).

In unadjusted analyses, an increased odds ratio for depression was observed for "other" work hours in unstratified (OR = 1.75, 95% CI = 1.21-2.51) and female (OR = 1.62, 95% CI = 1.05-2.51) models; in adjusted models these effects persisted but confidence intervals widened to non-significance at the p = 0.05 level. In models adjusted for previous depressive symptoms, females in "flexible/non-regulated" schedules showed an increased odds ratio for depression (OR = 2.01, 95% CI = 1.08-3.76), while a decreased odds ratio was observed for the unstratified model "regular shift work (no nights)" category (OR = 0.61; 95% CI = 0.38-0.97).

DISCUSSION

The Swedish Longitudinal Occupational Survey of Health (SLOSH) provided a unique opportunity to investigate the effects of work schedule. This survey's extensive information on working time was used to develop an exposure variable with eight work schedule categories, a unique level of detail that reduced the potential for misclassification bias. Its use of objective measures of antidepressant drug prescriptions from a comprehensive nation-wide registry further reduced the potential for subjective bias in reporting, the latter being particularly important for a widely stigmatized outcome such as mental health (25).

Shift work involving nights and early mornings is generally thought to confer the greatest risk of circadian disruption (35,36) and may negatively impact on mental health in a number of ways (9).

However, our results appear to suggest that other work scheduling factors play an important role in the development of depressive symptoms requiring pharmaceutical treatment.

In the final models adjusted for demographics, work, and prior symptoms of depression, the odds ratio for prospective antidepressant prescription = yes was significantly increased for females reporting flexible or non-regulated work hours (OR = 2.01; 95% CI = 1.08-3.76). There are two (non-exclusive) forms of flexible working time arrangements: organization-orientated flexibility, where the hours of work are determined by the employer (e.g. on-call work); and employee-orientated flexibility, which is associated with high levels of worktime control (21). Several strands of evidence suggest that employee-orientated flexibility was relatively high among those in the current sample working flexible or non-regulated hours. Work time control was higher in this category of work schedule than any other category (37). The proportion of respondents with managerial roles (generally associated with greater work time control) was substantially higher in this category of work schedule (57.8% of men and 43.9% of women) than in the entire SLOSH sample (43.9% and 27.2%, respectively). Typical occupational categories within this schedule category included several that are commonly associated with high levels of work time control and boundaryless working (i.e. where employees can decide for themselves when and where to work; (18)), namely legislators (22.4% of men and 10.0% of women), professionals (33.6% of men and 61.0% of women), and technical and associate professionals (27.3% of men and 12.8% of women). It therefore seems likely the respondents in this schedule category were often in positions of high responsibility and were more likely to be engaged in boundaryless work. While the potential negative effects of boundaryless work have been discussed elsewhere (21,20) the current study is the first to identify an association with objective measures of mental health. That the effect was greater among women is consistent with a scenario in which women with flexible work hours are more likely than men to use the flexibility to engage in additional non-work responsibilities, rather than using the increased control to fully recover and reduce strain outcomes (32). As well as leading to impaired recovery, such a scenario is also likely to be associated with greater work-life conflict for these women. Conflicts between work and home life can negatively affect marital relationships and parental roles, and may also lead to increased sleep problems, chronic fatigue, and psychosomatic symptoms (38), with potentially negative consequences for mental health (39).

In the final models adjusted for demographic, work, and prior symptoms of depression, the odds ratio for prospective antidepressant prescription was decreased for those reporting day and evening shift work in the non-stratified model (OR = 0.61, 95% CI = 0.38-0.97). (These effects did not reach significance in the sex-stratified models, possibly due to the relatively small sample sizes involved). In the Swedish population, regular shift work (in this case, without nights) schedules are known well in advance. It is possible that such schedules provide a protective effect on mental health due to greater flexibility to manage personal responsibilities outside of work. A similar finding was noted in a large Canadian survey of nurses, where individuals working "slow rotating" shifts (i.e., up to one change in shifts every 2 weeks) decreased the odds of depression, relative to regular day time workers (24).

Strengths and Limitations

The SLOSH is based on a nationally representative sample of the Swedish working population, therefore results are generalizable to a wide range of occupations. Antidepressant prescription rates in this study are comparable to other Nordic countries, further strengthening the generalizability of our results. For example, antidepressant prescription rates of 5.3% have been noted among public sector employees in Finland (40) and 6.5% in Denmark (41).

The SLOSH collected a breadth of detail on work and work schedule characteristics, such as weekly work hours, history of night work, and demand-control, social support, and emotional demands at work. However, other characteristics that have been linked with negative mental health outcomes, such as long weekly working hours (42), short shift durations (43), and the presence/characteristics of shift rotations (4,44,45) were not included, and should be considered in future studies.

This prospective study assessed antidepressant prescriptions in an approximately 2-year period following the assessment of work schedule in 2008, providing a stronger base for assessing causality as compared to a cross-sectional study design. Although a longer time lag would be necessary to reduce the possibility of reverse causality for chronic outcomes (such as cancer), depression is a relatively quick-onset disease, so a 2-year follow-up was deemed to be sufficient.

To further reduce the potential for reverse causality, prior depression and prior antidepressant prescriptions were controlled for in the final models.

Self-selection in to and out of certain types of work schedule, where differential movement of workers out of "harmful" schedules produces a workforce of shift workers that is healthier than day workers, is a common methodological challenge in shift work research (22). For example, recent longitudinal studies have shown that the presence of depressive symptoms (3) and other depression-related outcomes (46) at baseline is associated with a change in work schedule (leaving night work). This phenomenon tends to bias results toward underestimated effects, due to a diluted reference group that contains both day and former shift workers. While this "healthy worker" bias presents a challenge to any observational study, its impacts on observed effects can be better understood and accounted for using longitudinal study designs and information on past work history. In the current study, self-selection *out of* shift work was accounted for by creating a reference category of day workers with no prior history of working night shifts. This is a major strength compared to many other studies where self-selection bias is simply ignored, however it still does not account for primary self-selection *in to* shift work (e.g., at the start of an individual's working life). This "clean" reference group also implicitly assumes that night work is the most disruptive form of shift work with respect to mental health outcomes, which, as the current findings suggest, may not be the case. Despite these potential sources of misclassification, relationships between work schedule and antidepressant prescriptions were nonetheless observed in this study.

A strength of this study is the use of objective registry-based outcome measures, that are relatively rare in this area of the literature and may be used to support causal inference in an emerging area of shift work and health research (41). The Prescribed Drug Register provides good coverage of the Swedish population (47) and avoids issues of self-report bias. Our use of objective antidepressant prescriptions measures (that were recorded independently of survey participation) also precluded attrition-related bias, since outcomes were available regardless of participation in the subsequent survey wave.

Despite the benefits of this objective outcome measure, the use of antidepressant drug prescription rates as a proxy for mood disorders is associated with a number of limitations. First,

it should be acknowledged that various factors (e.g., treatment seeking behaviours, clinician recognition and treatment of depressive disorders) influence drug prescription statistics (48–50). Furthermore, not all individuals with depression or other mood disorders are treated with antidepressant medications (48,49). And finally, while antidepressant medications are primarily prescribed for the treatment of depression, they can also be used in the treatment of other mental disorders and somatic diseases such as sleeping problems, anxiety, or pain (48,51). This being said, the validity of using antidepressant medication prescriptions as an outcome measure (12-month prevalence of 6.0% in 2008) is strengthened by its comparability with a prior Swedish sample from Stockholm county, where 12-month prevalence of depressive disorders was reported among 4.1% of men and 6.6% of women (52).

Specifying work schedule in terms of eight exposure categories, along with the stratification by gender, meant that some cell sizes in the analyses were low. Thus it is possible that some of the non-significant associations were a result of inadequate statistical power.

Conclusions

This two-year prospective study addresses a number of known methodological issues in work schedule epidemiology through its use of a longitudinal design, detailed exposure assessment, health outcomes obtained from a national registry, and sex-stratified analyses. Findings indicate the presence of a relationship between work schedule and subsequent antidepressant medication prescriptions. A clearer understanding of work schedule's effects on mental health will be facilitated by additional research that builds upon the current study's strengths with inception cohorts and enhanced detail on work factors with potential impacts on mental health.

Author Contributions

CL participated in SLOSH data collection. ALH, GK, and PT conceptualized the current study design; ALH performed statistical analyses and drafted the manuscript. All authors participated in conceptualizing the current study, interpreting the data, and revising the manuscript.

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Conflicts of interests

The authors have no conflicts of interests to declare.

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Table 1: Baseline characteristics of study sample and univariate relationships with prospective antidepressant prescriptions (2008-2010)

	One or more antidepressants prescription registered between June 17, 2008 and Dec 31, 2010								
	All			Female			Male		
	Total (%)	*No (%)*	*Yes (%)*	*Total (%)*	*No (%)*	*Yes (%)*	*Total (%)*	*No (%)*	*Yes (%)*
Total	8643 (100)	7883 (91.2)	760 (8.8)	4663 (100)	4132 (88.6)	531 (11.4)	3980 (100)	3751 (94.2)	229 (5.8)
Work Schedule, 2008									
Regular days (no hx night work)	5786	5294 (91.5)	492 (8.5)	3190	2842 (89.1)	348 (10.9)	2596	2452 (94.5)	144 (5.5)
Regular days (≤ 3 yrs night work hx)	568	516 (90.8)	52 (9.2)	253	222 (87.7)	31 (12.3)	315	294 (93.3)	21 (6.7)
Regular days (4+ yrs night work hx)	520	472 (90.8)	48 (9.2)	196	174 (88.8)	22 (11.2)	324	298 (92.0)	26 (8.0)
Nights (regular, roster or rotating)	580	534 (92.1)	46 (7.9)	282	251 (89.0)	31 (11.0)	298	283 (95.0)	15 (5.0)
Regular shift work, days and evenings only	377	348 (92.3)	29 (7.7)	229	204 (89.1)	25 (10.9)	148	144 (97.3)	4 (2.7)
Roster work, days and evenings only	296	262 (88.5)	34 (11.5)	233	202 (86.7)	31 (13.3)	63	60 (95.2)	3 (4.8)
Flexible/non-regulated hours	258	235 (91.1)	23 (8.9)	123	106 (86.2)	17 (13.8)	135	129 (95.6)	6 (4.4)
Other work hours	258	222	36	157	131	26	101	91	10

		(86.0)	(14.0)		(83.4)	(16.6)		(90.1)	(9.9)
Sex									
Female	4663	4132 (88.6)	531 (11.4)						
Male	3980	3751 (94.2)	229 (5.8)						
Age Group									
20-35 years	1244	1161 (93.3)	83 (6.7)	640	582 (90.9)	58 (9.1)	604	579 (95.9)	25 (4.1)
36-50 years	3424	3105 (90.7)	319 (9.3)	1897	1672 (88.1)	225 (11.9)	1527	1433 (93.8)	94 (6.2)
51-70 years	3975	3617 (91.0)	358 (9.0)	2126	1878 (88.3)	248 (11.7)	1849	1739 (94.1)	110 (5.9)
Chronotype									
Distinctly or somewhat a morning person	3317	3058 (92.2)	259 (7.8)	1859	1675 (90.1)	184 (9.9)	1458	1383 (94.9)	75 (5.1)
Neither	2274	2051 (90.2)	223 (9.8)	1244	1076 (86.5)	168 (13.5)	1030	975 (94.7)	55 (5.3)
Distinctly or somewhat an evening person	3052	2774 (90.9)	278 (9.1)	1560	1381 (88.5)	179 (11.5)	1492	1393 (93.4)	99 (6.6)
Significant Other Status									
Single	1817	1618 (89.0)	199 (11.0)	1023	875 (85.5)	148 (14.5)	794	743 (93.6)	51 (6.4)
Married/cohabitating	6826	6265 (91.8)	561 (8.2)	3640	3257 (89.5)	383 (10.5)	3186	3008 (94.4)	178 (5.6)
Education									
Compulsory	1229	1094 (89.0)	135 (11.0)	622	530 (85.2)	92 (14.8)	607	564 (92.9)	43 (7.1)
Upper Secondary/Vocational Training	4076	3764 (92.3)	312 (7.7)	1933	1725 (89.2)	208 (10.8)	2143	2039 (95.1)	104 (4.9)
University or Equivalent	3338	3025 (90.6)	313 (9.4)	2108	1877 (89.0)	231 (11.0)	1230	1148 (93.3)	82 (6.7)
Chronic Conditions									
None	5741	5330 (92.8)	411 (7.2)	3132	2833 (90.5)	299 (9.5)	2609	2497 (95.7)	112 (4.3)
1 or more	2902	2553 (88.0)	349 (12.0)	1531	1299 (84.8)	232 (15.2)	1371	1254 (91.5)	117 (8.5)
Employer Type									
Private company	4064	3775 (92.9)	289 (7.1)	1499	1345 (89.7)	154 (10.3)	2565	2430 (94.7)	135 (5.3)
Other (Association/Non-profit, Own business/Farm, or other)	780	715 (91.7)	65 (8.3)	367	327 (89.1)	40 (10.9)	413	388 (93.9)	25 (6.1)
Government (local, district, or central)	3799	3393 (89.3)	406 (10.7)	2797	2460 (88.0)	337 (12.0)	1002	933 (93.1)	69 (6.9)
Work Hours									
8-31 hours/week	1244	1047 (84.2)	197 (15.8)	993	829 (83.5)	164 (16.5)	251	218 (86.9)	33 (13.1)
≥ 32 hours/week	7399	6836 (92.4)	563 (7.6)	3670	3303 (90.0)	367 (10.0)	3729	3533 (94.7)	196 (5.3)
Demand-Control at Work									
Low Demands, Low Control	2068	1919 (92.8)	149 (7.2)	1122	1014 (90.4)	108 (9.6)	946	905 (95.7)	41 (4.3)

High Demands, Low Control	1568	1391 (88.7)	177 (11.3)	897	762 (84.9)	135 (15.1)	671	629 (93.7)	42 (6.3)
Low Demands, High Control	2533	2310 (91.2)	223 (8.8)	1299	1153 (88.8)	146 (11.2)	1234	1157 (93.8)	77 (6.2)
High Demands, High Control	2474	2263 (91.5)	211 (8.5)	1345	1203 (89.4)	142 (10.6)	1129	1060 (93.9)	69 (6.1)
Social Support at Work									
Low	4531	4107 (90.6)	424 (9.4)	2367	2076 (87.7)	291 (12.3)	2164	2031 (93.9)	133 (6.1)
High	4112	3776 (91.8)	336 (8.2)	2296	2056 (89.5)	240 (10.5)	1816	1720 (94.7)	96 (5.3)
Emotional Demands at work									
Often or sometimes	4427	3967 (89.6)	460 (10.4)	2888	2526 (87.5)	362 (12.5)	1539	1441 (93.6)	98 (6.4)
Seldom or never	4216	3916 (92.9)	300 (7.1)	1775	1606 (90.5)	169 (9.5)	2441	2310 (94.6)	131 (5.4)
Depression in 2008 or Antidepressant prescription 2005-2008									
No	7542	7292 (96.7)	250 (3.3)	3895	3740 (96.0)	155 (4.0)	3647	3552 (97.4)	95 (2.6)
Yes	1101	591 (53.7)	510 (46.3)	768	392 (51.0)	376 (49.0)	333	199 (59.8)	134 (40.2)

Table 2: Unadjusted and Adjusted Logistic Regression Odds Ratios and Confidence Intervals (Modeling Antidepressant Prescriptions 2008-2010 = Yes)

	Unadjusted			Adjusted for Demographic + Work Variables			Adjusted for Demographic + Work Variables + Previous Depression or Antidepressants		
	All	**Females**	**Males**	**All**	**Females**	**Males**	**All**	**Females**	**Males**
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Shift Work Schedule, 2008									
Regular days	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Regular days (≤ 3 yrs hx night work)	1.08 (0.80-1.46)	1.14 (0.77-1.69)	1.22 (0.76-1.95)	1.10 (0.81-1.50)	1.03 (0.69-1.54)	1.28 (0.79-2.07)	0.90 (0.63-1.29)	0.73 (0.46-1.18)	1.23 (0.71-2.14)
Regular days (4+ yrs hx night work)	1.09 (0.80-1.49)	1.03 (0.65-1.63)	1.49 (0.96-2.29)	1.11 (0.81-1.53)	0.93 (0.58-1.47)	1.31 (0.84-2.05)	1.01 (0.70-1.47)	0.64 (0.37-1.10)	1.54 (0.93-2.56)
Flexible/non-regulated hours	1.05 (0.68-1.63)	1.31 (0.78-2.21)	0.79 (0.34-1.83)	1.08 (0.69-1.69)	1.36 (0.80-2.34)	0.67 (0.29-1.57)	1.49 (0.90-2.47)	**2.01 (1.08-3.76)**	0.88 (0.35-2.24)
Nights (regular, roster or regular shift work)	0.93 (0.68-1.27)	1.01 (0.68-1.49)	0.90 (0.52-1.56)	0.76 (0.55-1.06)	0.74 (0.49-1.12)	0.84 (0.48-1.48)	0.95 (0.65-1.38)	1.01 (0.63-1.63)	0.85 (0.45-1.59)
Other work hours	**1.75 (1.21-2.51)**	**1.62 (1.05-2.51)**	1.87 (0.95-3.67)	1.41 (0.97-2.05)	1.32 (0.85-2.07)	1.63 (0.81-3.28)	1.47 (0.93-2.32)	1.39 (0.81-2.40)	1.72 (0.75-3.94)
Shift work (days & evenings only)	0.90 (0.61-1.32)	1.00 (0.65-1.54)	0.47 (0.17-1.30)	0.72 (0.48-1.08)	0.78 (0.50-1.21)	0.52 (0.19-1.44)	**0.61 (0.38-0.97)**	0.62 (0.37-1.05)	0.50 (0.17-1.49)
Roster work (days & evenings only)	1.40 (0.97-2.02)	1.25 (0.85-1.86)	0.85 (0.26-2.75)	0.94 (0.64-1.39)	0.92 (0.61-1.40)	0.92 (0.28-3.01)	1.02 (0.65-1.61)	0.97 (0.60-1.57)	1.08 (0.28-4.14)
Sex									
Male	-	-	-	Ref	-	-	Ref	-	-
Female	-	-	-	**1.77 (1.48-2.12)**	-	-	**1.36 (1.11-1.67)**	-	-
Age Group									
20-35 years		-	-	Ref	Ref	Ref	Ref	Ref	Ref
36-50 years		-	-	**1.30 (1.01-1.68)**	1.24 (0.91-1.70)	1.55 (0.98-2.47)	1.11 (0.83-1.49)	1.05 (0.73-1.50)	1.31 (0.78-2.18)
51-70 years		-	-	1.04 (0.80-1.36)	1.02 (0.74-1.40)	1.14 (0.71-1.84)	1.01 (0.75-1.36)	0.97 (0.67-1.39)	1.13 (0.67-1.91)
Chronotype									
Distinctly or somewhat a morning person		-	-	Ref	Ref	Ref	Ref	Ref	Ref
Distinctly or somewhat an evening person		-	-	**1.27 (1.06-1.52)**	1.21 (0.97-1.51)	1.37 (1.00-1.88)	1.15 (0.93-1.42)	1.15 (0.89-1.50)	1.12 (0.78-1.60)
Neither		-	-	**1.33 (1.10-1.61)**	**1.46 (1.16-1.83)**	1.05 (0.73-1.52)	1.17 (0.94-1.46)	**1.35 (1.03-1.76)**	0.83 (0.55-1.25)
Significant Other Status									

Married/cohabitating	-	-	Ref	Ref	Ref	Ref	Ref	Ref
Single	-	-	**1.40 (1.17-1.66)**	**1.50 (1.22-1.85)**	1.19 (0.85-1.65)	1.13 (0.92-1.39)	1.22 (0.95-1.57)	0.99 (0.68-1.43)
Education								
Compulsory	-	-	Ref	Ref	Ref	Ref	Ref	Ref
Upper Secondary/Vocational	-	-	**0.77 (0.61-0.96)**	0.79 (0.60-1.05)	0.71 (0.48-1.04)	0.77 (0.59-1.00)	**0.70 (0.50-0.98)**	0.84 (0.55-1.30)
University or Equivalent	-	-	0.85 (0.67-1.08)	0.82 (0.61-1.09)	0.94 (0.62-1.44)	0.87 (0.66-1.15)	0.81 (0.57-1.14)	1.02 (0.64-1.63)
Chronic Conditions								
None	-	-	Ref	Ref	Ref	Ref	Ref	Ref
1 or more	-	-	**1.70 (1.45-1.99)**	**1.58 (1.30-1.91)**	**1.95 (1.47-2.58)**	**1.51 (1.26-1.82)**	**1.38 (1.10-1.74)**	**1.81 (1.32-2.49)**
Employer Type								
Private company	-	-	Ref	Ref	Ref	Ref	Ref	Ref
Government (local, district, or central)	-	-	1.09 (0.91-1.32)	1.04 (0.83-1.31)	1.17 (0.84-1.63)	1.06 (0.85-1.30)	1.06 (0.81-1.38)	1.03 (0.71-1.49)
Other (Association/Non-profit, Own business/Farm, Other)	-	-	1.00 (0.74-1.33)	0.94 (0.64-1.38)	1.00 (0.63-1.58)	0.90 (0.64-1.26)	0.92 (0.59-1.43)	0.89 (0.53-1.50)
Work Hours								
≥ 32 hours/week	-	-	Ref	Ref	Ref	Ref	Ref	Ref
8-31 hours/week	-	-	**1.90 (1.58-2.29)**	**1.79 (1.46-2.21)**	**2.50 (1.64-3.81)**	**1.66 (1.33-2.07)**	**1.66 (1.29-2.12)**	**1.77 (1.07-2.92)**
Demand-Control at Work								
High Demands, Low Control	-	-	Ref	Ref	Ref	Ref	Ref	Ref
High Demands, High Control	-	-	**0.78 (0.62-0.98)**	**0.70 (0.54-0.92)**	1.02 (0.67-1.55)	0.86 (0.66-1.12)	0.77 (0.55-1.06)	1.07 (0.67-1.71)
Low Demands, High Control	-	-	0.86 (0.69-1.08)	0.80 (0.61-1.05)	1.04 (0.69-1.58)	1.10 (0.84-1.43)	1.05 (0.76-1.46)	1.20 (0.75-1.93)
Low Demands, Low Control	-	-	**0.67 (0.53-0.85)**	**0.67 (0.50-0.89)**	0.69 (0.44-1.10)	0.79 (0.60-1.05)	0.81 (0.58-1.13)	0.75 (0.45-1.26)
Social Support at Work								
High	-	-	Ref	Ref	Ref	Ref	Ref	Ref
Low	-	-	1.12 (0.96-1.32)	1.12 (0.92-1.35)	1.12 (0.85-1.50)	0.94 (0.78-1.13)	0.94 (0.75-1.18)	0.90 (0.65-1.24)
Emotional Demands at Work								
Seldom or never	-	-	Ref	Ref	Ref	Ref	Ref	Ref
Often or sometimes	-	-	1.19 (1.00-1.42)	**1.29 (1.04-1.61)**	1.05 (0.78-1.41)	1.04 (0.85-1.27)	1.15 (0.89-1.49)	0.85 (0.61-1.20)
Prior Depression (2008) or Prior Antidepressant Prescription (2005-2008)								
No						Ref	Ref	Ref
Yes						**23.0 (19.2-27.5)**	**23.3 (18.6-29.1)**	**24.2 (17.7-33.1)**

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	10-12
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7, 16-18
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	16-18
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 19-20
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The effect of work schedule on prospective antidepressant prescriptions in Sweden: A 2-year sex-stratified analysis using national drug registry data

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MANUSCRIPT TITLE

The effect of work schedule on prospective antidepressant prescriptions in Sweden: A 2-year sex-stratified analysis using national drug registry data

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ABSTRACT

INTRODUCTION

Depression-related mood disorders affect millions of people worldwide and contribute to substantial morbidity and disability, yet little is known about the effects of work scheduling on depression. This study used a large Swedish survey to prospectively examine the effects of work schedule on registry-based antidepressant prescriptions in females and males over a two-year period.

METHODS

The study was based on an approximately representative sample (n=3980 males, 4663 females) of gainfully employed participants in the Swedish Longitudinal Occupational Survey of Health. Sex-stratified and unstratified analyses were conducted using logistic regression. For exposure, 8 categories described work schedule in 2008: “regular days” (3 categories of night work history:

none, ≤ 3 years, 4+ years), “night shift work”, “regular shift work (no nights)”, “rostered work (no nights)”, “flexible/non-regulated hours”, and “other”. For the primary outcome measure, all prescriptions coded N06A according to the Anatomical Therapeutic Chemical System were obtained from the Swedish National Prescribed Drug Register and dichotomized into “any” or “no” prescriptions between 2008 and 2010. Estimates were adjusted for potential sociodemographic, health, and work confounders, and for prior depressive symptoms.

RESULTS

In 2008, 22% of females versus 19% of males worked outside of regular daytime schedule. Registered antidepressant prescription rates in the post-survey period were 11.4% for females versus 5.8% for males. In fully adjusted models, females in “flexible/non-regulated” schedules showed an increased odds ratio for prospective antidepressant prescriptions (OR=2.01, 95% CI=1.08-3.76). In males, odds ratios were most increased in those working “other” schedules (OR=1.54, 95% CI=0.93-2.56) and “Regular days with 4 or more years’ history of night work” (OR=1.72, 95% CI=0.75-3.94).

CONCLUSIONS

This study’s findings support a relationship between work schedule and prospective antidepressant prescriptions in the Swedish workforce. Future research should continue to assess sex-stratified relationships, using detailed shift work exposure categories and objective registry data where possible.

Article Summary

Strengths and Limitations

- Two-year longitudinal design
- Based on a large national survey (the Swedish Longitudinal Occupational Survey of Health) with detailed information on workplace, demographic, and social characteristics

- Addresses a number of common methodological limitations in shift work research through its use of detailed exposure assessment, objectively recorded health outcome measures, and sex-stratified analyses
- Other characteristics that have been linked with negative mental health outcomes, such as long weekly working hours, short shift durations, and the presence/characteristics of shift rotations should also be considered in future studies

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INTRODUCTION

An individual's work schedule characteristics may bear an important influence on their mental health. On the one hand, high levels of work time control have been linked to positive health outcomes such as affective wellbeing and perceived stress. On the other hand, shift work has been linked to increased symptoms of depression and negative mood compared to regular day work (1–4). Shift workers may be at increased risk of developing mental disorders such as depression due to biological and social disturbances that are caused by their work schedules (5,6). Sleep disturbances in shift workers are well documented (7–9); these represent the most widely reported circadian disruptions associated with depression (10). Exposure to light-at-night has also been linked to mental health effects, both directly and through its suppression of melatonin (11–13). Finally, the social zeitgeber theory postulates that stressful life events may trigger depressive episodes by disrupting social routines (6).

Depressive disorders are prevalent in western countries (14), and contribute to substantial morbidity and disability worldwide (15,16). However, studies of the association between work schedule and clinically verified mental illness such depression remain relatively scarce. Furthermore, methodological challenges are an important limitation when examining associations between work schedule and mental health (17). First, a lack of clear and well defined exposure

definitions increase the potential for measurement error and misclassification (18) bias that have been shown to attenuate effect estimates in prior studies of shift work and depression (19). Second, mental health outcomes are often measured through subjective reporting, that is more susceptible to bias compared to objective health outcome data, particularly given the social stigma attached to poor mental health (20). Thirdly, sex-stratified analyses are biologically valid and important to conduct yet this is not always done; an important consideration since both work schedule (21) and rates of reported depressive disorders (16) are known to differ across males and females. There is some evidence of differential impacts of shift work on mental health by sex (22,23) although the evidence is inconsistent across studies. Finally, self-selection of individuals in to and out of jobs with non-standard work hours (the "healthy worker effect") can bias results toward underestimated effects and is particularly problematic when past exposures are not accounted for.

To address these challenges, the present study utilized data from the Swedish Longitudinal Occupational Survey of Health (SLOSH) (24). This large national survey collected detailed information on workplace, demographic, and social characteristics, and can be linked to national health registries in Sweden. We examined the prospective effect of work schedule (using detailed categories that considered prior night work history) on antidepressant prescription rates (using objective measures obtained via linkage to a national health registry), in females and in males, over a two-year period.

Shift work, especially where it involves night work, could be expected to be associated with higher rates of antidepressant prescription, due to the chronic disruption of circadian rhythms, sleep and social routines. Female shift workers are expected to show higher prescription rates than their male counterparts, due to the double burden of shift working and family responsibilities (25), higher emotional job demands (26), and possible psychobiological gender differences in the impact of circadian disruption (27). The impact of flexible work hours on antidepressant prescription rates is more difficult to predict. While having control over one's work hours is potentially beneficial, it may also lead to overwork. Thus, no predictions were made with respect to associations between flexible work and antidepressant prescription rates.

METHODS

Patient and Public Involvement

This study is based on an approximately representative sample of gainfully employed Swedish individuals participating in the Swedish Longitudinal Occupational Survey of Health (SLOSH). The SLOSH is a follow-up of Swedish Work Environment Survey (SWES) participants, a biennial sample of gainfully employed individuals drawn from the Swedish Labor Force Survey. The general aim of the SLOSH is to investigate longitudinal relationships between work environment (in particular psychosocial), labour market participation, health, and well-being, among others.

The SLOSH was approved by the Stockholm Regional Research Ethics Board. Participants were not directly involved in any part of the current study, but gave informed consent to participate through their response to the SLOSH questionnaires. Participants are informed about research results by means of a public web page: www.slosh.se.

Study Sample

The baseline study sample was drawn from the n = 9756 participants who were currently working in the 2008 SLOSH survey wave (this wave was chosen since it yielded a relatively large number of respondents, and collected information on history of night work). This sample was limited to respondents who provided valid answers for work schedule (excluded n = 195), who did not work a regular evening schedule due to small numbers in this category (excluded n = 58), who worked between 8 and 70 hours per week (excluded n = 25 reporting fewer than 8 hours per week, n = 12 reporting more than 70 hours per week, and n = 355 with missing data), and who provided valid answers for all other variables included in the models. This produced an analytic sample of n = 8643 respondents in the 2008 SLOSH wave.

Primary exposure and outcome

Eight categories were used to describe work schedule in 2008: “regular days with no history of night work”, “regular days with history of night work ≤ 3 years”, “regular days with history of night work ≥ 4 years”, “night work (regular, rostered, or rotating)”, “regular shift work (no nights)”, “rostered work (no nights)”, “flexible/non-regulated hours”, and “other”. Regular shift work involves working a set of invariantly timed shifts that cycle according to fixed sequence.

Rostered work also involves invariantly timed shifts, but the sequence is more ad hoc such that the employee has relatively short notice of which shifts they will be working. Flexible / non-regulated hours involves duty-periods that could vary both with respect to the start and finish times, and which days are worked.

Data on antidepressant medication prescriptions were obtained from the Swedish National Prescribed Drug Register. This register contains information on all prescribed drugs dispensed from Swedish pharmacies since July 2005 (except for those given in hospitals or nursing homes). This data was anonymously linked to survey respondents through registered personal identification numbers. All Drug Register prescriptions coded N06A according to the Anatomical Therapeutic Chemical System (World Health Organization, 2017) were extracted for the analysis. A dichotomous variable ("yes" or "no" was created to describe any antidepressant prescriptions registered between June 17, 2008 and December 31, 2010, representing a period of approximately 2.5 years following the 2008 survey wave. June 17 2008 represents the date on which 75% of responses were received from the 2008 SLOSH wave participants.

Analyses

Logistic regression models were used to examine the prospective association between work schedule reported in 2008 and subsequent antidepressant prescriptions for males and females separately. Model estimates were adjusted for the potentially confounding effects of other variables hypothesized as being risk factors for depression and also related to work schedule (see Table 1 for detail).

Demographic & social variables included age, chronotype, significant other status, education, and the presence of chronic conditions, while work variables included employer type, weekly number of hours worked, emotional demands at work, demand-control at work, and social support at work.

Previous depression and/or previous antidepressant prescriptions was described with two categories: "yes" and "no". SLOSH respondents were assigned "yes" if they reported depression in the prior SLOSH wave as assessed with the Symptom Checklist-core depression (SCL-CD6) (28), or if they had been prescribed any antidepressant medications (prescriptions coded N06A) in the

Swedish National Prescribed Drug Register in the three years prior to the 2008 SLOSH wave (July 1, 2005 to June 17, 2008).

Demographic, work variables, and previous depression and/or previous antidepressant prescription variables were entered sequentially as covariates to examine how these factors affected the effect estimates.

RESULTS

Table 1 summarizes variables within the study sample (n = 8643). Females represented 54% of the total sample. The majority of all respondents (n = 6874, or 80%) reported regular daytime work in 2008; of these, n = 1088 (16%) had previously worked nights. For females, n = 3639 (78%) reported regular daytime work in 2008; of these, n = 449 (12%) had previously worked nights. For males, n = 3235 (81%) reported regular daytime work in 2008; of these, n = 639 (20%) had previously worked nights. Registered antidepressant prescription rates in the post-survey period were 11.4% for females versus 5.8% for males. The highest rates of registered antidepressant prescriptions occurred in both females and males reporting "other" work hours. For females, this was followed by "flexible/non-regulated" hours and "roster work, days and evenings only". For males, this was followed by "regular days (4+ years of night work history)" and "regular days (3 years or less of night work history).

In unadjusted analyses (Table 2), an increased odds ratio for depression was observed for "other" work hours in the male (OR = 1.87 , 95% CI = 0.95-3.67) and female (OR = 1.62, 95% CI = 1.05-2.51) models; in adjusted models these effects persisted but confidence intervals widened to non-significance at the p = 0.05 level for both sexes. In models adjusted for previous depressive symptoms, females in "flexible/non-regulated" schedules showed an increased odds ratio for depression (OR = 2.01, 95% CI = 1.08-3.76), while the strongest increases in males were observed for those working "other" schedules (OR=1.54, 95% CI=0.93-2.56) and "Regular days with 4 or more years' history of night work" (OR=1.72, 95% CI=0.75-3.94).

DISCUSSION

The Swedish Longitudinal Occupational Survey of Health (SLOSH) provided a unique opportunity to investigate the effects of work schedule. This survey's extensive information on working time was used to develop an exposure variable with eight work schedule categories, a unique level of detail that reduced the potential for misclassification bias. Its use of objective measures of antidepressant drug prescriptions from a comprehensive nation-wide registry further reduced the potential for subjective bias in reporting, the latter being particularly important for a widely stigmatized outcome such as mental health (20).

Shift work involving nights and early mornings is generally thought to confer the greatest risk of circadian disruption (29,30) and may negatively impact on mental health in a number of ways (5). However, our results suggest that other work scheduling factors also play an important role in the development of depressive symptoms requiring pharmaceutical treatment.

In the final models adjusted for demographics, work, and prior symptoms of depression, the strongest effect for prospective antidepressant prescription = yes was observed in females reporting flexible or non-regulated work hours (OR = 2.01; 95% CI = 1.08-3.76). There are two (non-exclusive) forms of flexible working time arrangements: organization-orientated flexibility, where the hours of work are determined by the employer (e.g. on-call work); and employee-orientated flexibility, which is associated with high levels of worktime control (31). Several strands of evidence suggest that employee-orientated flexibility was relatively high among those in the current sample working flexible or non-regulated hours. Work time control was higher in this category of work schedule than any other category (32). The proportion of respondents with managerial roles (generally associated with greater work time control) was substantially higher in this category of work schedule (57.8% of males and 43.9% of females) than in the entire SLOSH sample (43.9% and 27.2%, respectively). Typical occupational categories within this schedule category included several that are commonly associated with high levels of work time control and boundaryless working (i.e. where employees can decide for themselves when and where to work (33)); namely legislators (22.4% of males and 10.0% of females), professionals (33.6% of males and 61.0% of females), and technical and associate professionals (27.3% of males and 12.8% of females). It therefore seems likely the respondents in this schedule category were often in positions of high responsibility and were more likely to be engaged in boundaryless work.

High levels of work time control have been shown to positively influence mental health outcomes such as affective wellbeing and perceived stress (34). The potentially beneficial effects of allowing employees control over their work hours has been ascribed to the promotion of a positive balance between effort and recovery, and between work and non-work life (34). However, the flexibility of boundaryless work may also have negative consequences (35). When workloads are high and there are ambiguous norms about work hours, there the employee may feel pressured to restructure their personal time to work, resulting in overwork (36). Mixing work and family time may also produce difficulties "switching off" thoughts of work, such that work never stops, thereby increasing stress and impeding recovery (31).

While the potential negative effects of boundaryless work have been discussed elsewhere (31,36) the current study is the first to identify an association with objective measures of mental health. That the effect was greater among females is consistent with a scenario in which females with flexible work hours are more likely than males to use the flexibility to engage in additional non-work responsibilities, rather than using the increased control to fully recover and reduce strain outcomes (37). As well as leading to impaired recovery, such a scenario is also likely to be associated with greater work-life conflict that can negatively affect marital relationships and parental roles, and may also lead to increased sleep problems, chronic fatigue, and psychosomatic symptoms (38), with potentially negative consequences for mental health (39).

Strengths and Limitations

The SLOSH is based on a nationally representative sample of the Swedish working population, therefore results are generalizable to a wide range of occupations. Antidepressant prescription rates in this study are comparable to other Nordic countries, further strengthening the generalizability of our results. For example, antidepressant prescription rates of 5.3% have been noted among public sector employees in Finland (40) and 6.5% in Denmark (41).

The SLOSH collected a breadth of detail on work and work schedule characteristics, such as weekly work hours, history of night work, and demand-control, social support, and emotional demands at work. However, other characteristics that have been linked with negative mental health outcomes, such as long weekly working hours (42), short shift durations (43), and the

presence/characteristics of shift rotations (4,44,45) were not included, and should be considered in future studies. This prospective study assessed antidepressant prescriptions in an approximately 2-year period following the assessment of work schedule in 2008, providing a stronger base for assessing causality as compared to a cross-sectional study design. Although a longer time lag would be necessary to reduce the possibility of reverse causality for chronic outcomes (such as cancer), depression is a relatively quick-onset disease, so a 2-year follow-up was deemed to be sufficient.

To further reduce the potential for reverse causality, the final models were adjusted for prior depression (as reported in the 2006 SLOSH) and prior antidepressant prescriptions in the 3 years prior to the 2008 SLOSH. While restriction to individuals without a prior history of depression or antidepressant prescriptions would have been most appropriate for an inception cohort, this is not the case with the SLOSH, where individuals worked various types of schedules prior to their participation in the survey. If a "clean" cohort had been assumed (i.e., if prior exposures and outcomes at a participant's time of entry into the SLOSH were ignored), and work schedule affected antidepressant prescription rates, the effect of work schedule on antidepressant prescription rates would be underestimated (to what extent is unknown). The exclusion of over 1000 individuals with prior depression/antidepressant prescriptions would also have precluded the use of detailed exposure categories (results not shown), a major goal of these analyses. For these reasons, adjustment was applied rather than restriction. This may have resulted in residual confounding, given the strength of the association with prior depression or prior antidepressant prescription (see Table 2).

Self-selection in to and out of certain types of work schedule, where differential movement of workers out of “harmful” schedules produces a workforce of shift workers that is healthier than day workers, is a common methodological challenge in shift work research (17). For example, recent longitudinal studies have shown that the presence of depressive symptoms (3) and other depression-related outcomes (46) at baseline is associated with a change in work schedule (leaving night work). This phenomenon tends to bias results toward underestimated effects, due to a diluted reference group that contains both day and former shift workers. While this “healthy worker” bias presents a challenge to any observational study, its impacts on observed effects can

be better understood and accounted for using longitudinal study designs and information on past work history. In the current study, self-selection *out of* shift work was accounted for by creating a reference category of day workers with no prior history of working night shifts. This is a major strength compared to many other studies where self-selection bias is simply ignored, however it still does not account for primary self-selection *in to* shift work (e.g., at the start of an individual's working life). This "clean" reference group also implicitly assumes that night work is the most disruptive form of shift work with respect to mental health outcomes, which, as the current findings suggest, may not be the case. Despite these potential sources of misclassification, relationships between work schedule and antidepressant prescriptions were nonetheless observed in this study.

A strength of this study is the use of objective registry-based outcome measures, that are relatively rare in this area of the literature and may be used to support causal inference in an emerging area of shift work and health research (41). The Prescribed Drug Register provides good coverage of the Swedish population (47) and avoids issues of self-report bias. Our use of objective antidepressant prescriptions measures (that were recorded independently of survey participation) also precluded attrition-related bias, since outcomes were available regardless of participation in the subsequent survey wave. However, the cutpoint used to assess prospective antidepressant use (the date on which 75% of responses were received from participants in the 2008 SLOSH wave) may have introduced a small degree of misclassification, e.g., if any of the 25% remaining individuals were prescribed antidepressants after the cutpoint but prior to submitting their survey responses.

Despite the benefits of this objective outcome measure, the use of antidepressant drug prescription rates as a proxy for mood disorders is associated with a number of limitations. First, it should be acknowledged that various factors (e.g., treatment seeking behaviours, clinician recognition and treatment of depressive disorders) influence drug prescription statistics (48–50). Furthermore, not all individuals with depression or other mood disorders are treated with antidepressant medications (48,49). And finally, while antidepressant medications are primarily prescribed for the treatment of depression, they can also be used in the treatment of other mental disorders and somatic diseases such as sleeping problems, anxiety, or pain (48,51). This being

said, the validity of using antidepressant medication prescriptions as an outcome measure (12-month prevalence of 6.0% in 2008) is strengthened by its comparability with a prior Swedish sample from Stockholm county, where 12-month prevalence of depressive disorders was reported among 4.1% of males and 6.6% of females (52).

Specifying work schedule with eight exposure categories, along with the stratification by gender, meant that some cell sizes in the analyses were low. Thus it is possible that some of the non-significant associations were a result of inadequate statistical power.

Conclusions

This two-year prospective study addresses a number of known methodological issues in work schedule epidemiology through its use of a longitudinal design, detailed exposure assessment, health outcomes obtained from a national registry, and sex-stratified analyses. Findings indicate the presence of a relationship between work schedule and subsequent antidepressant medication prescriptions. A clearer understanding of work schedule's effects on mental health will be facilitated by additional research that builds upon the current study's strengths with inception cohorts and enhanced detail on work factors with potential impacts on mental health.

Author Contributions

CL participated in SLOSH data collection. ALH, GK, and PT conceptualized the current study design; ALH performed statistical analyses and drafted the manuscript. All authors participated in interpreting the data and revising the manuscript.

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Data sharing statement

Due to legal restrictions, the SLOSH data cannot be made publicly available. We are not permitted to share the data set underlying our findings since this would compromise the integrity and privacy of study participants. For data requests please contact the SLOSH data manager Constanze Leineweber at constanze.leineweber@su.se.

Conflicts of interests

The authors have no conflicts of interests to declare.

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Table 1: Baseline characteristics of study sample and univariate relationships with prospective antidepressant prescriptions (2008-2010)

	One or more antidepressants prescription registered between June 17, 2008 and Dec 31, 2010					
	Female			**Male**		
	Total (%)	*No (%)*	*Yes (%)*	*Total (%)*	*No (%)*	*Yes (%)*
Total	4663 (100)	4132 (88.6)	531 (11.4)	3980 (100)	3751 (94.2)	229 (5.8)
Work Schedule, 2008						
Regular days (0 yrs hx night work)	3190	2842 (89.1)	348 (10.9)	2596	2452 (94.5)	144 (5.5)

Regular days (≤ 3 yrs night work hx)	253	222 (87.7)	31 (12.3)	315	294 (93.3)	21 (6.7)
Regular days (4+ yrs night work hx)	196	174 (88.8)	22 (11.2)	324	298 (92.0)	26 (8.0)
Nights (regular, roster or rotating)	282	251 (89.0)	31 (11.0)	298	283 (95.0)	15 (5.0)
Regular shift work, days and evenings only	229	204 (89.1)	25 (10.9)	148	144 (97.3)	4 (2.7)
Roster work, days and evenings only	233	202 (86.7)	31 (13.3)	63	60 (95.2)	3 (4.8)
Flexible/non-regulated hours	123	106 (86.2)	17 (13.8)	135	129 (95.6)	6 (4.4)
Other work hours	157	131 (83.4)	26 (16.6)	101	91 (90.1)	10 (9.9)
Age Group						
20-35 years	640	582 (90.9)	58 (9.1)	604	579 (95.9)	25 (4.1)
36-50 years	1897	1672 (88.1)	225 (11.9)	1527	1433 (93.8)	94 (6.2)
51-70 years	2126	1878 (88.3)	248 (11.7)	1849	1739 (94.1)	110 (5.9)
Chronotype						
Distinctly or somewhat a morning person	1859	1675 (90.1)	184 (9.9)	1458	1383 (94.9)	75 (5.1)
Neither	1244	1076 (86.5)	168 (13.5)	1030	975 (94.7)	55 (5.3)
Distinctly or somewhat an evening person	1560	1381 (88.5)	179 (11.5)	1492	1393 (93.4)	99 (6.6)
Significant Other Status						
Single	1023	875 (85.5)	148 (14.5)	794	743 (93.6)	51 (6.4)
Married/cohabitating	3640	3257 (89.5)	383 (10.5)	3186	3008 (94.4)	178 (5.6)
Education						
Compulsory	622	530 (85.2)	92 (14.8)	607	564 (92.9)	43 (7.1)
Upper Secondary/Vocational Training	1933	1725 (89.2)	208 (10.8)	2143	2039 (95.1)	104 (4.9)
University or Equivalent	2108	1877 (89.0)	231 (11.0)	1230	1148 (93.3)	82 (6.7)
Chronic Conditions [1]						
None	3132	2833 (90.5)	299 (9.5)	2609	2497 (95.7)	112 (4.3)
1 or more	1531	1299 (84.8)	232 (15.2)	1371	1254 (91.5)	117 (8.5)
Employer Type						
Private company	1499	1345 (89.7)	154 (10.3)	2565	2430 (94.7)	135 (5.3)
Other (Association/Non-profit, Own business/Farm, or other)	367	327 (89.1)	40 (10.9)	413	388 (93.9)	25 (6.1)
Government (local, district, or central)	2797	2460 (88.0)	337 (12.0)	1002	933 (93.1)	69 (6.9)
Work Hours						

8-31 hours/week	993	829 (83.5)	164 (16.5)	251	218 (86.9)	33 (13.1)
≥ 32 hours/week	3670	3303 (90.0)	367 (10.0)	3729	3533 (94.7)	196 (5.3)
Demand-Control at Work [2]						
Low Demands, Low Control	1122	1014 (90.4)	108 (9.6)	946	905 (95.7)	41 (4.3)
High Demands, Low Control	897	762 (84.9)	135 (15.1)	671	629 (93.7)	42 (6.3)
Low Demands, High Control	1299	1153 (88.8)	146 (11.2)	1234	1157 (93.8)	77 (6.2)
High Demands, High Control	1345	1203 (89.4)	142 (10.6)	1129	1060 (93.9)	69 (6.1)
Social Support at Work [2]						
Low	2367	2076 (87.7)	291 (12.3)	2164	2031 (93.9)	133 (6.1)
High	2296	2056 (89.5)	240 (10.5)	1816	1720 (94.7)	96 (5.3)
Emotional Demands at work [3]						
Often or sometimes	2888	2526 (87.5)	362 (12.5)	1539	1441 (93.6)	98 (6.4)
Seldom or never	1775	1606 (90.5)	169 (9.5)	2441	2310 (94.6)	131 (5.4)
Depression in 2008 or Antidepressant prescription 2005-2008						
No	3895	3740 (96.0)	155 (4.0)	3647	3552 (97.4)	95 (2.6)
Yes	768	392 (51.0)	376 (49.0)	333	199 (59.8)	134 (40.2)

[1] Based on the questions "Has a doctor told you that you have": "heart disease", "diabetes", "rheumatic disorder", "musculoskeletal disorder", "obstructive pulmonary disease", or "asthma"
[2] Based on the 17-question Swedish Demand-Control-Support Questionnaire (DCSQ) scale (53)
[3] Based on the question "Does your work put you in emotionally disturbing situations?"

Table 2: Unadjusted and Adjusted Logistic Regression Odds Ratios and Confidence Intervals (Modeling Antidepressant Prescriptions 2008-2010 = Yes)

	Unadjusted		Adjusted for Demographic + Work Variables		Adjusted for Demographic + Work Variables + Previous Depression or Antidepressants	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Work Schedule, 2008						
Regular days (0 yrs hx night work)	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Regular days (≤ 3 yrs hx night work)	1.14 (0.77-1.69)	1.22 (0.76-1.95)	1.03 (0.69-1.54)	1.28 (0.79-2.07)	0.74 (0.46-1.18)	1.23 (0.71-2.14)
Regular days (4+ yrs hx night work)	1.03 (0.65-1.63)	1.49 (0.96-2.29)	0.93 (0.58-1.47)	1.31 (0.84-2.05)	0.64 (0.37-1.10)	1.54 (0.93-2.56)
Flexible/non-regulated hours	1.31 (0.78-2.21)	0.79 (0.34-1.83)	1.36 (0.80-2.34)	0.67 (0.29-1.57)	**2.01 (1.08-3.76)**	0.88 (0.35-2.24)
Nights (regular, roster or regular shift work)	1.01 (0.68-1.49)	0.90 (0.52-1.56)	0.74 (0.49-1.12)	0.84 (0.48-1.48)	1.01 (0.63-1.63)	0.85 (0.45-1.59)
Other work hours	**1.62 (1.05-2.51)**	1.87 (0.95-3.67)	1.32 (0.85-2.07)	1.63 (0.81-3.28)	1.39 (0.81-2.40)	1.72 (0.75-3.94)
Shift work (days & evenings only)	1.00 (0.65-1.54)	0.47 (0.17-1.30)	0.78 (0.50-1.21)	0.52 (0.19-1.44)	0.64 (0.37-1.05)	0.50 (0.17-1.49)
Roster work (days & evenings only)	1.25 (0.85-1.86)	0.85 (0.26-2.75)	0.92 (0.61-1.40)	0.92 (0.28-3.01)	0.97 (0.60-1.57)	1.08 (0.28-4.14)
Age Group						
20-35 years	-	-	Ref	Ref	Ref	Ref
36-50 years	-	-	1.24 (0.91-1.70)	1.55 (0.98-2.47)	1.05 (0.73-1.50)	1.31 (0.78-2.18)
51-70 years	-	-	1.02 (0.74-1.40)	1.14 (0.71-1.84)	0.97 (0.67-1.39)	1.13 (0.67-1.91)
Chronotype						
Distinctly or somewhat a morning person	-	-	Ref	Ref	Ref	Ref
Distinctly or somewhat an evening person	-	-	1.21 (0.97-1.51)	1.37 (1.00-1.88)	1.16 (0.89-1.50)	1.12 (0.78-1.60)
Neither	-	-	**1.46 (1.16-1.83)**	1.05 (0.73-1.52)	**1.35 (1.03-1.76)**	0.83 (0.55-1.25)
Significant Other Status						
Married/cohabitating	-	-	Ref	Ref	Ref	Ref
Single	-	-	**1.50 (1.22-1.85)**	1.19 (0.85-1.65)	1.23 (0.95-1.57)	0.99 (0.68-1.43)
Education						

Compulsory	-	-	Ref	Ref	Ref	Ref
Upper Secondary/Vocational	-	-	0.79 (0.60-1.05)	0.71 (0.48-1.04)	**0.70 (0.50-0.98)**	0.84 (0.55-1.30)
University or Equivalent	-	-	0.82 (0.61-1.09)	0.94 (0.62-1.44)	0.81 (0.57-1.14)	1.02 (0.64-1.63)
Chronic Conditions						
None	-	-	Ref	Ref	Ref	Ref
1 or more	-	-	**1.58 (1.30-1.91)**	**1.95 (1.47-2.58)**	**1.38 (1.10-1.74)**	**1.81 (1.32-2.49)**
Employer Type						
Private company	-	-	Ref	Ref	Ref	Ref
Government (local, district, or central)	-	-	1.04 (0.83-1.31)	1.17 (0.84-1.63)	1.06 (0.81-1.38)	1.03 (0.71-1.49)
Other (Association/Non-profit, Own business/Farm, Other)	-	-	0.94 (0.64-1.38)	1.00 (0.63-1.58)	0.91 (0.59-1.43)	0.89 (0.53-1.50)
Work Hours						
≥ 32 hours/week	-	-	Ref	Ref	Ref	Ref
8-31 hours/week	-	-	**1.79 (1.46-2.21)**	**2.50 (1.64-3.81)**	**1.66 (1.29-2.12)**	**1.77 (1.07-2.92)**
Demand-Control at Work						
High Demands, Low Control	-	-	Ref	Ref	Ref	Ref
High Demands, High Control	-	-	**0.70 (0.54-0.92)**	1.02 (0.67-1.55)	0.78 (0.55-1.06)	1.07 (0.67-1.71)
Low Demands, High Control	-	-	0.80 (0.61-1.05)	1.04 (0.69-1.58)	1.05 (0.76-1.46)	1.20 (0.75-1.93)
Low Demands, Low Control	-	-	**0.67 (0.50-0.89)**	0.69 (0.44-1.10)	0.81 (0.58-1.13)	0.75 (0.45-1.26)
Social Support at Work						
High	-	-	Ref	Ref	Ref	Ref
Low	-	-	1.12 (0.92-1.35)	1.12 (0.85-1.50)	0.94 (0.75-1.18)	0.90 (0.65-1.24)
Emotional Demands						
Seldom or never	-	-	Ref	Ref	Ref	Ref
Often or sometimes	-	-	**1.29 (1.04-1.61)**	1.05 (0.78-1.41)	1.15 (0.89-1.49)	0.85 (0.61-1.20)
Prior Depression (2008) or Prior Antidepressant Prescription (2005-2008)						
No					Ref	Ref
Yes					**23.3 (18.6-29.1)**	**24.2 (17.7-33.1)**

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	10-12
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7, 16-18
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	16-18
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 19-20
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.