# The Influence of Shift Work on Early Reproductive Outcomes: A Meta-Analysis

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| AuthorsStocker LJ 1 Registrar in Obstetrics and GynaecologyMacklon NS 1 Professor of Obstetrics and GynaecologyBewley S 2 Professor of Complex ObstetricsCheong YC 1 Senior Lecturer in Obstetrics and Gynaecology1 University of Southampton, Faculty of Medicine, Academic Unit of Human Development and Health, SO16 5YA (UK)2 Kings College London, Women’s AcademicHealth Centre, c/o 10th Floor, St Thomas' Hospital, Westminster Bridge Road, SE1 7EH (UK)Corresponding author:Dr Linden Stocker Room F86, Level F Princess Anne Hospital, Southampton, SO16 5YA02380 796033l.stocker@soton.ac.ukMain text word count: 3766Funding: No funding was received.AbstractBottom of Form |

## Objective

To determine whether an association exists between shift work and early reproductive outcomes (menstrual disruption, subfertility or miscarriage).

## Data sources

Extensive electronic databases searches on Medline, Embase and Web of Science. Additional sources included Google scholar, the Cochrane library database and online publications of national colleges and references of retrieved papers.

## Methods of Study Selection

Included studies compared female shift workers with non-shift workers who suffered adverse early reproductive events.

## Tabulation, integration and results

Two independent reviewers extracted adjusted and raw data. Random effect models were used to pool data, weighting for the inverse of the variance. Assessments of heterogeneity, bias and subgroup analyses were performed. 16 independent cohorts from 15 studies including 123 403 women were subject to analysis. Unadjusted data showed shift workers had increased rates of menstrual disruption (n=71 681, OR 1.22, 95%CI 1.15-1.29, I2 0%) and subfertility (n=28 479, OR 1.80, 95%CI 1.01-3.19 I2 94%) but not miscarriage (n=19 553, OR 0.95, 95%CI 0.86-1.05, I2 0%). Night shifts wereassociated with increased miscarriage rates (n=13 018, OR 1.29, 95%CI 1.11-1.50, I2 0%).Confounders-adjustment led to persistent relationships between shift work and menstrual dysfunction (OR 1.15 95%CI 1.01-1.31, I2 70%) but not subfertility (OR 1.11 95%CI 0.86-1.44, I2 61%). The association between night shifts and miscarriage remained (OR 1.41 95%CI 1.22-1.63, I2 0%).

## Conclusion

Shift work is associated with increased rates of menstrual disruption and miscarriage. Whether a direct effect or mediated by confounders, it may have implications for policy makers, employers and the reproductive health of women working shifts.

Word count of abstract: 254

# Introduction

Women are integral to the workforce and contribute significantly to the world economy ([1](#_ENREF_1)). They account for almost half the working population in the United Kingdom, and the majority are of reproductive age ([2](#_ENREF_2)).

Shift work occurs across all occupations and social classes ([2](#_ENREF_2)). In the current environment almost 20% of women perform duties outside standard hours (generally between 0800 and 1800), most for the entirety of their working lives ([2](#_ENREF_2)). Shift work constitutes a risk factor for disease by causing alterations to psychological, social and biological functioning. This manifests in increased rates of cardiovascular disease, ([3](#_ENREF_3)) metabolic disturbances and cancer ([4](#_ENREF_4)).

Previous reviews have revealed associations between shift work and increased risks of preterm birth, low birth weight and fetal loss ([5-7](#_ENREF_5)), whilst others have focused on exposure to occupational hazards ([8](#_ENREF_8)). However, the impact of shift work on early reproductive outcomes is still largely unknown.

### Objectives

To determine whether there is an association between shift work and early reproductive outcomes.

# Sources

A systematic review was performed according to a predetermined protocol and reported in accordance with Meta-analysis Of Observational Studies In Epidemiology ([9](#_ENREF_9)).

All human studies that may have described shift work and menstrual disorders, subfertility and pregnancy loss until July 2013 were eligible with no restriction on publication date, study design status or language (initially search was limited to English language, but a subsequent unrestricted search was performed). We contacted authors of published studies for clarification of specifics where necessary. No formal attempt was made to retrieve unpublished data.

Two authors (LS, YC) performed an electronic database search (see supplementary material) and reviewed all titles/abstracts of returned articles, resolving discrepancies by arbitration. We hand searched references and contacted experts to obtain additional data where required. We combined search terms with Boolean logic and used special features to identify synonyms and broaden the search.

# Study selection

### Exposure and participants

Women from any occupation were included. Shift work was defined as work executed outside normal working hours (0800-1800). The comparison group were women with normal working hours or who did not work (Table 1). The number of subjects in each group had to be known.

### Outcome

1. Menstrual dysfunction/deregulation

A short (< 25 days) or long cycle (>31 days) ([10](#_ENREF_10)), excluding studies describing ‘irregularity’ or changes in cycle length.

1. Subfertility

Time-to-pregnancy interval exceeding 12 months ([11](#_ENREF_11)) (studies reporting number of menstrual cycles had to be quantified in months).

1. Miscarriage

Spontaneous loss of pregnancy before 24 completed weeks ([12](#_ENREF_12)). We included data if the definition of miscarriage was fewer, but not greater than 24 completed weeks of pregnancy. Terminations of pregnancy were excluded.

Two authors (LS, YC) screened all studies, reviewing full papers where required and disregarding those ineligible. Authors were contacted if it was impossible to extract or calculate numbers from the data and where fruitless, we excluded the study. Compliant subsets of data were included from larger series. Discrepancies were resolved by arbitration.

### Data extraction

Two authors (LS, YC) independently extracted data with a template adapted from the Cochrane Collaboration ([13](#_ENREF_13)), solving disputes by arbitration. Authorships and data sources were scrutinised to prevent data duplication. Original numbers were extracted for consistency of data handling. Where available adjusted effect measures (odds ratios, relative risks and risk ratios with 95%CI or p values) were recorded.

Two authors (LS, YC) independently rated quality using the Newcastle–Ottawa scale ([14](#_ENREF_14)), as recommended by Cochrane ([13](#_ENREF_13)). Points were awarded in three domains: study group selection, comparability of the groups and ascertainment of outcome. Studies were graded low, intermediate or high quality by the percentage of possible points scored (1-33%, 34-66%, 67-100% respectively). Low-quality studies/those not achieving one point in each domain were excluded. Disagreements were resolved by mediation.

### Statistical methods

#### Exposure effect

RevMan software version 5.1 was used to combine studies, calculating odds ratios (OR) and 95%CIs for individual study results. Meta analyses were performed using fixed- (Mantel-Haenszel) ([15](#_ENREF_15)) and random-effects methods (DerSimonian and Laird) ([16](#_ENREF_16)) reporting both when conclusions differed without substantial heterogeneity.In the adjusted analyses we preferentially pooled multivariable adjusted risk estimates. Units of analysis were number of women (menstrual disruption and subfertility) or pregnancies (miscarriage).

#### Heterogeneity

The I2 test was used to identify inter-study variation, with results denoting low (<25%), medium (25-50%), high (50%-74%), or considerable (>75%) heterogeneity ([13](#_ENREF_13), [17](#_ENREF_17)). In cases of high/considerable heterogeneity, random-effects analyses were reported.

### Predetermined subgroup/sensitivity analysis

As night shifts have been hypothesised to produce poorer outcomes ([18](#_ENREF_18)) we performed subgroup analyses on women only working nights (see supplementary material). Pooled estimates were subjected to influence-analyses of study design, size and confounders to confirm robustness and identify sources of heterogeneity/bias. If adjusted data was available we calculated the natural logarithms of the effect measure and corresponding standard errors; otherwise we included the unadjusted estimate. Pooled adjusted and unadjusted data were weighted for the inverse of the variance.

# Results

See Figure 1. The 15 included studies are shown in Table 1. All data were dichotomous.

All 15 included studies had a parallel design: 8 cross sectional ([19-26](#_ENREF_19)), 2 case control ([27](#_ENREF_27), [28](#_ENREF_28)) and 5 cohort studies (three prospective ([29-31](#_ENREF_29)) two retrospective ([32](#_ENREF_32), [33](#_ENREF_33)) ). 12 countries were represented (largely USA and Europe) although two were from Taiwan and one Thailand (Table 1).

#### Participants

Table 1 shows the characteristics of the 123 403 included women; 71 681 reporting on menstrual disturbances, 28 479 on subfertility and 23 243 on miscarriage (from 23 611

pregnancies).

One subfertility used two populations of women; a ‘pregnancy’ and a ‘population’ group ([22](#_ENREF_22)). There were significant differences in each arm of the study design so we treated the data as two entities (Bisanti 1996 (1) ‘population group’ and Bisanti 1996 (2) ‘pregnancy group’), hereafter referred to separately and bringing the number of included cohorts to 16.

Nine of the 15 included studies had a primary objective of assessing the effect of shift work on early reproductive outcomes ([20-22](#_ENREF_20), [24](#_ENREF_24), [25](#_ENREF_25), [30](#_ENREF_30), [33](#_ENREF_33), [34](#_ENREF_34)) (22 1&2). Five examined shifts as one of various work-related risks ([19](#_ENREF_19), [27-29](#_ENREF_27), [31](#_ENREF_31), [32](#_ENREF_32)) and one as subgroup analyses ([23](#_ENREF_23)) (Table 1.).

Employed women were the comparison group in 11 cohorts; eight matched for occupation ([19](#_ENREF_19), [20](#_ENREF_20), [25](#_ENREF_25), [28-30](#_ENREF_28), [32](#_ENREF_32), [34](#_ENREF_34)). Of the three unmatched cohorts, one compared office and factory workers ([21](#_ENREF_21)) and two used mixed occupations ([27](#_ENREF_27), [33](#_ENREF_33)) (Table 1.). Four studies ([22-24](#_ENREF_22), [31](#_ENREF_31)) (22 1&2) combined working and non-working women as comparison groups.

### Outcomes

### Quality

No studies were rejected due to poor quality. 14/15 {Bisanti, 1996 #100}([19-24](#_ENREF_19), [27-30](#_ENREF_27), [32-34](#_ENREF_32))(1) were of high and two of medium quality ([22](#_ENREF_22), [25](#_ENREF_25))(2) (supplementary material).

### Bias

All studies scored 50% or above for ‘selection’. Blinding was not possible for the case-control studies. Performance bias was most likely in studies including non-working women in comparison groups ([22-24](#_ENREF_22), [31](#_ENREF_31)) (22 1&2), but was otherwise low. Despite efforts to contact authors who may have had includable data, not all were contactable so data was excluded ([35](#_ENREF_35), [36](#_ENREF_36)) (a potential n=579, 2% of the total women in the subfertility group, and n=698, 4% in the miscarriage group). Response rates were >85% in three studies, 75-84% in nine studies and 50%-74% in two studies and the multi-country cohorts reported ranges of 54-88% ([22](#_ENREF_22))(1) and 70-98% ([22](#_ENREF_22))(2). Three miscarriage studies ascertained differences between the outcomes of women who responded ([27](#_ENREF_27), [28](#_ENREF_28), [34](#_ENREF_34)) with higher rates (88.4% vs 81.4%) ([27](#_ENREF_27)) from women not miscarrying, although similar complete data (87.8% vs 87.1%) ([28](#_ENREF_28)). There were higher miscarriage rates in the non-responders ([34](#_ENREF_34)) (11.3% vs 9.9%) suggesting that women suffering poor outcome were less likely to engage. It cannot be determined whether this applies with menstrual disruption or subfertility.

Outcome was determined by telephone ([33](#_ENREF_33)), face-to-face interviews ([22-24](#_ENREF_22))(1), diary keeping ([19](#_ENREF_19), [29](#_ENREF_29)), data directly from medical records/discharge registers ([27](#_ENREF_27), [28](#_ENREF_28), [31](#_ENREF_31)) or written questionnaire ([20](#_ENREF_20), [22](#_ENREF_22), [25](#_ENREF_25), [30](#_ENREF_30), [32](#_ENREF_32))(2). One study used monthly installments ([21](#_ENREF_21)) and one checked medical records ([34](#_ENREF_34)). The minority relied upon written recall alone, minimizing detection bias.

Exposure was assessed by questionnaire in 14 studies. One asked employers to complete this information ([28](#_ENREF_28)), and two confirmed the participant-provided information by referencing employment records ([34](#_ENREF_34)), and asking women to keep a contemporaneous diary ([19](#_ENREF_19)), thus minimizing reporting bias. Those studies assessing working pattern by recall alone used written questionnaires ([20-22](#_ENREF_20), [25](#_ENREF_25), [29](#_ENREF_29), [30](#_ENREF_30), [32](#_ENREF_32))(2), face-to-face interviews ([22-24](#_ENREF_22))(1), telephone interview ([27](#_ENREF_27), [31](#_ENREF_31), [33](#_ENREF_33)) or a combination of diaries and written questionnaires ([19](#_ENREF_19)) (Table 1).

Publication bias was not formally measured nor meta-regression performed because the number of studies (fewer than 10) for comparison within each outcome was small ([13](#_ENREF_13)).

3/4 menstrual disruption studies excluded women using hormonal contraception or endocrine disturbances ([20](#_ENREF_20), [21](#_ENREF_21), [29](#_ENREF_29)). One study made no mention of this in their methods, potentially including women with endocrine manipulation or pathology ([19](#_ENREF_19)). 4/5 fertility studies ([22-24](#_ENREF_22), [33](#_ENREF_33))(2) included only women who had conceived a pregnancy, not accounting for women who were infertile. 3/6 miscarriage studies excluded terminations, ectopic and multiple pregnancies ([30-32](#_ENREF_30)). One study excluded women with recurrent miscarriage ([25](#_ENREF_25)) and one with pregnancies affected by congenital malformations ([28](#_ENREF_28)), slightly altering total pregnancy rates.

### The effect of shift work

### Menstrual disruption

Four pooled studies ([19](#_ENREF_19), [29](#_ENREF_29), [32](#_ENREF_32), [33](#_ENREF_33)) showed an un weighted rate of menstrual disruption of between 13.4% (955/71 077)([20](#_ENREF_20)) and 43.5% (130/329)([21](#_ENREF_21)). Women working shifts had an increased rate of menstrual disruption in the unadjusted analysis (OR 1.22 95%CI 1.15-1.29, I2 0%) (Figure 2).

The effect of night shift work was non-significant in the unadjusted subgroup of women who worked nights (10/28) compared with women who did not work shifts (39/155). However, heterogeneity was substantial and the analysis included only small numbers (n=183, OR 1.72, 95%CI 0.33-8.95, I2 69%) (Figure 2).

### Fertility

Five cohorts showed an un weighted subfertility rate of between 10.5% (295/3 092)([22](#_ENREF_22))(1) to 16.3% (135/907)([24](#_ENREF_24)). Women working shifts had higher rates of subfertility (529/4 668, 11.3%) than women who did not (2 354/23 811, 9.9%) (OR 1.80 95%CI 1.01-3.20, I2 94%) with considerable heterogeneity (Figure 2). Only one cohort ([22](#_ENREF_22))(1) included women who had not managed to conceive a pregnancy (n = 3 092 OR 2.54 95%CI 1.73-3.74).

Only one study provided data for a mutually exclusive group of night shift workers so subgroup analysis assessing the effect of night shifts on subfertility were not possible. There were higher rates of subfertility in night shift workers compared with women not working shifts (29/177, 16.6% vs 1 797/17 531, 10.3% crude OR 1.72, 95%CI 1.15-2.56).

###  Miscarriage

The combined data from seven studies showed an un weighted rate of miscarriage of between 10.1% (410/4051)([31](#_ENREF_31)) and 35.4% (432/1341)([27](#_ENREF_27)) with no difference in miscarriage rates in shift workers (939/7 931, 12.0%) vs non-shift workers (1 898/15 673, 12.1%) (OR 0.96, 95%CI 0.88-1.05, I2 0%)(Figure 2).

The subgroup analysis of 13 018 women from five studies showed a significantly increased rate of miscarriage in night shift workers compared with non-shift workers (237/1 823, 13.0% vs 1 201/11 195, 10.7% OR 1.29 95%CI 1.11-1.50, I2 0%) (Figure 2).

### Sensitivity analysis

***Heterogeneity***

Heterogeneity was generally low excepting for the subfertility group (I2 94%). Cohorts were removed sequentially to investigate individual study effects. Two cohorts ([24](#_ENREF_24), [33](#_ENREF_33)) not specifying the period of exposure dramatically affected the I2 value for the shift work comparison (OR 2.75 95%CI 2.02-3.75, I2 30%). Data interrogation of the menstrual disorders subgroup was not possible in this manner (only two cohorts).

#### Large studies

We omitted a large study (n= 71 077)([20](#_ENREF_20)) in the shift work and menstrual disruption analysis and the relationship remained stable (n=604 OR 1.56 95%CI 1.04-2.34, 12 0%). Similarly, when removing a particularly large cohort (n=21 438) ([33](#_ENREF_33)) from the subfertility analysis, the association with shift work persisted (OR 2.16 95%CI 1.33-3.50, I2 80%).

#### Study design

Restriction to cross sectional studies ([19-21](#_ENREF_19)) suggested no significant menstrual disturbance in shift workers (n= 71 557 OR 1.33, 95%CI 1.00-1.75, I2 33%). Subfertility rates remained increased, but this comparison is equivalent to removing the large aforementioned study (n=7780 OR 2.16 95%CI 1.33-3.50, I2 80%). No other study design analyses were possible.

Restriction to cross sectional studies ([25](#_ENREF_25), [34](#_ENREF_34)) showed no effect of shift (n=2 418 OR 1.06 95%CI 0.79-1.42, I2 0%) nor night work (n=1 090, OR 1.08 0.74-1.59 I2 0%) on miscarriage rates. Similarly, neither case-control ([27](#_ENREF_27), [28](#_ENREF_28)) nor cohort studies ([30-32](#_ENREF_30)) of shift work had an impact (n=1 965, OR 0.86 95%CI 0.66 -1.12 I2 24%; and n=21 639, OR 0.98 95%CI 0.89 -1.08 I2 0% respectively). However, cohort designs ([30](#_ENREF_30), [32](#_ENREF_32)) showed an augmented effect of night work on miscarriage rate (n=11 695 OR 1.33 95%CI 1.12 -1.58 I2 0%).

#### Eligibility

One study defined miscarriage as pregnancies ending before 28 weeks gestation ([34](#_ENREF_34)), stating that 99% of these occurred at fewer than 16 weeks but the authors were unable to provide the number of pregnancy losses between 25-28 weeks. This would have been a maximum of seven women and calculation demonstrated no impact on overall effect. Thus, this initially excluded study was retained. Excluding this study did not alter results for the shift workers’ comparison (n= 18 846 OR 0.94 95%CI 0.85-1.04, I2 0%) nor the subgroup of night workers (n=12 634 OR 1.29 95%CI 1.10 -1.51 I2 0%).

The menstrual disturbances study not specifying hormonal manipulation or disturbance ([19](#_ENREF_19)) was removed in a sensitivity analysis, and the result was stable (n=71 681 OR 1.22 95%CI 1.15-1.29 I2 0%).

#### Confounders

***Menstrual disruption***

Two studies provided adjusted effect measures ([20](#_ENREF_20), [21](#_ENREF_21)) (Table 2). Pooled multivariable analysis using adjusted risk estimates when available showed the effect of shift work remained significant (OR 1.15 95%CI 1.01-1.31, I2 70%) but not when restricting to adjusted data (OR 1.12 95% CI 0.99-1.25 I2 75%) (Figure 2). This comparison was not possible for the subgroup of night workers.

***Subfertility***

All cohorts provided adjusted effect measures (Table 2). Pooled analysis was non significant (OR 1.11 95%CI 0.86-1.44, I2 61%) (Figure2), remaining similar with exclusion of the study reporting individual effect measures depending on type of shift worked (OR 1.25 95%CI 0.82-1.91)([33](#_ENREF_33)) and in the one cohort ([22](#_ENREF_22))(1) providing data for women not managing to conceive (n= 3 092 OR 1.2 95%CI 0.2-8.3). This comparison was not possible for the cohorts of night workers (n = 2 cohorts).

***Miscarriage***

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| Six studies provided effect measures for confounders ([25](#_ENREF_25), [27](#_ENREF_27), [28](#_ENREF_28), [30](#_ENREF_30), [31](#_ENREF_31), [34](#_ENREF_34)) (Table 2). When pooling these the effect of shift work remained non-significant (OR 1.04 95%CI 0.89-1.22, I2 43%). In a pooled multivariable analysis using adjusted risk estimates where available, the effect of night work was still significant (OR 1.41 95%CI 1.22-1.63, I2 0%) with similar results if only adjusted data was used (n= 3 cohorts, OR 1.40 95%CI 1.07-1.82 I2 29%) (Figure 2). |

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# Conclusion

### Summary

Shift work is significantly associated with early reproductive outcomes. Increased rates of menstrual disruption and subfertility are found in women who work shifts. There is no difference in miscarriage rates in women who work ‘generic’ shifts, but there is an association in those women who work nights compared with women not working shifts. We found concordance across statistical models and types of study design. Adjusting for confounders led to an attenuated association for menstrual disruption, removed the association with subfertility but had no impact on the relationship with miscarriage.

### Strengths

We combined comprehensive searching, robust data synthesis methods and a validated quality assessment tool in order to produce a strong methodological approach. Analysis included large numbers of women from varying countries, cultures and occupations, increasing generalizability to study populations worldwide. We used unadjusted data to ensure standardization across pooled datasets and included adjusted analysis for comparison where possible. Current practices for meta-analysis and systematic review were adhered to, including specificity of search strategy, assessment of heterogeneity and subgroup analysis. Included studies appear to incur low risks of bias and be methodologically strong.

###  Limitations and bias

Differences between studies persist despite use of strict inclusion criteria and standardized unadjusted data. The exposure to shift work, type and duration, varied between studies. This compromise was inevitable because different national policies and cultural variation mean that subtle differences exist. The primary literature, in both human and animal studies, fails to consistently address the distinction between constant and fluctuating shifts. A recent review of miscarriage in shift workers ([8](#_ENREF_8)) and some of the included studies (Table 1) tried to circumvent this problems by stratifying data accordingly, but this invariably means narrowing inclusion criteria and number of studies without necessarily comparing equivalent shifts. Definitions of these shifts will still vary across the globe and limiting the search in this way will compromise breadth of data and application of results. The type of work performed outside standard working hours may be identical in certain jobs, for example continuous process industries. The intensity or type of work may differ in other roles, for example a preponderance of stressful emergency work at night, or a much lighter workload. By including a variety of types of work and (both manual workers and professional women) we ensured coverage of the broad nature of shift work.

Outcomes varied somewhat between studies (Table 1); this may have contributed to heterogeneity. We were unable to discern any major sources for the heterogeneity seen in subfertility. Only one cohort included women who had not conceived, rendering analyses susceptible to underestimation of effects by excluding women with sterility and sub fertile women not actively trying to conceive.

Adjusting for confounders produced attenuated results. This could demonstrate that shift work selects for risk factors and poor lifestyle habits. However, increased rates of adverse outcomes were still evident in studies adjusting for unhealthy behavior ([20-22](#_ENREF_20), [24](#_ENREF_24), [25](#_ENREF_25), [30](#_ENREF_30), [34](#_ENREF_34))(22 1&2). Studies adjusted for different risk factors, both lifestyle and demographic differences (Table 2). We did not have individual participant data; this would enable standardized comparisons of inherent discrepancies. Given these caveats, the ability of our data to clearly demonstrate that shift work confers an effect, or whether due to residual confounders, remains elusive.

### Interpretation

Available data suggests that shift work is a risk factor for health and reproductive functioning. Our review provides supporting evidence for a detrimental effect on early reproductive outcomes, consistent with previous studies in later pregnancy ([5](#_ENREF_5), [6](#_ENREF_6)).

The length of exposure of women to shift work was variable. It is possible that prolonged exposure might amplify any effects. A recent study found that there was an association of shift work and breast cancer, only becoming apparent after ≥30 years (OR 2.21, 95% CI 1.14 to 4.31) ([37](#_ENREF_37))). Exposure to shift work is unlikely to exist over such time periods in a reproduction review but duration may still be relevant in reproductive pathology.

The majority of women included in this review were in paid employment. Other work parameters, for example stress and exposure to environmental agents may confound results. By contrast, the ‘Healthy Worker Effect’ (“the consistent tendency of the actively employed to have a more favorable mortality experience than the population at large”), ([38](#_ENREF_38)) may impact on our findings. Working populations may exclude the severely ill or disabled, and working women may be better informed, or able to afford a better quality of life. Additionally, women who do not adapt well to shift work, may self-select jobs with routine hours ([18](#_ENREF_18)). These effects would attenuate our results.

It is likely that the observed effects are multifactorial, mediated by medical, social, psychological and demographic factors that are over represented or unique to shift workers ([39](#_ENREF_39)). For example, body mass index ([40](#_ENREF_40)), caffeine ([41](#_ENREF_41)) nicotine and drug use ([42-44](#_ENREF_42))), exercise levels ([45](#_ENREF_45)), and diet ([46](#_ENREF_46)) are risk factors for adverse reproductive functioning. Shift workers are exposed to these modifiers more than the general population ([3](#_ENREF_3), [18](#_ENREF_18)). However the majority of cohorts provided adjusted risks, suggesting that confounders do not solely account for the crude risk estimates.

Despite extensive publications on the health effects of shift work, little is known regarding the mechanisms. The greatest physiological problem is that sleeping phases are changed in relation to working times and daylight. Internal timekeeping is maintained in 24-hour oscillations of physiological responses, despite an out-of-synchronicity with the external environment ([47](#_ENREF_47)). If circadian disruption persists long term, altered physiology such as blood pressure and hormone production, result ([48](#_ENREF_48)). Exogenous changes to these processes are produced by altered light-dark cycles and also by working schedules. In females, circadian control is found throughout the hypothalamic-pituitary axis, playing a role in the timing of ovulation and progesterone secretion ([49](#_ENREF_49)). If reliant on circadian timings, disruption to this system could cause deleterious reproductive effects. Individual differences in circadian ‘typology’ affect biological functioning in health and disease and diurnal ‘preference’ may be modified by environmental factors ([50](#_ENREF_50)). Without individual patient data we cannot quantify individual adaptations to shift work, further confounding our results.

It cannot be concluded that early reproductive outcomes would be lessened by not performing shift work because no interventional trials exist. Nevertheless, if replicated our findings have implications for those attempting pregnancy as well as employers. These results will be of particular interest to couples hoping to achieve successful pregnancy but there is also evidence that menstrual cycle function may affect chronic disease risk ([51](#_ENREF_51)). The magnitude of the results should not be overstated. Any increases in adverse reproductive outcomes mediated by shift work will be small relative to the background risk. Up to 44% of women experience menstrual disruption ([52](#_ENREF_52)), 14% of couples subfertility ([11](#_ENREF_11)), and 20% of pregnancies end in miscarriage ([53](#_ENREF_53)). Thus if a woman experiences these outcomes, it is unlikely to be related to shift work and she should be advised that there are established, readily modifiable risk factors with proven and wide-reaching benefits.

Whilst the disruptive effects of shift work cannot be negated, coping strategies should be utilised. Working patterns allowing adequate recovery between shifts have been facilitated by the European Working Time Directive ([54](#_ENREF_54)) and heightened awareness of working womens’ rights ([55](#_ENREF_55)). Employers may accommodate women by modifying working hours, but ‘reproductive friendly’ hours have yet to be established. Indeed, for many women shift work has financial and social benefits.

Future research should be performed to validate these findings, stratifying results to examine whether increased years of shift working is associated with outcome. Whilst prospective long-term cohort studies would produce more meaningful results, cross sectional or retrospective studies of individual participant data would provide useful information. Ways to modulate circadian deregulation should also be investigated.

### Conclusion

This meta-analysis of observational studies, examining large numbers of women across diverse nationalities, cultures and social groups revealed an association of shift work and adverse early reproductive problems. These findings should be interpreted with caution because the data available is unable to isolate the role of shift work in comparison with other factors. However, the information may be valuable for individuals, employers and policy makers.

### Disclosure of interests

No authors have financial or non-financial interests that may be relevant to the submitted work.

### Contribution to authorship

LJS developed the idea and search strategy, identified studies, performed data extraction, analysis and interpretation and wrote the manuscript. YC contributed to identifying studies for inclusion, interpretation of data and revision of the manuscript. NM and SB revised the manuscript critically, contributed to interpretation of data and all authors approved the version for publication.

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

### Ethical approval

None required.

### List of tables, figures and supplementary files

**Table 1:** Included studies

**Table 2:** Adjusted data

**Figure 1:** Flow diagram

Flow diagram describing data selection

Adapted from: Moher, D et al., Preferred Reporting items for systematic reviews and meta‐analyses: the PRISMA statement. PLoS Med, 2009. 6(7)

**Figure 2:** Forest plots; comparisons of shift workers and non-shift workers

1 Menstrual dysfunction

1A Comparison of shift work with non-shift work: outcome menstrual cycle disruption (unadjusted)

1B Comparison of shift work with non-shift work: outcome menstrual cycle disruption (adjusted)

1C Comparison of night work with non-shift work: outcome menstrual cycle disruption

2 Subfertility

2A Comparison of shift work with non-shift work: outcome subfertility (unadjusted)

2B Comparison of shift work with non-shift work: outcome subfertility (adjusted)

3 Miscarriage

3A Comparison of shift work with non-shift work: outcome miscarriage (unadjusted)

3B Comparison of shift work with non-shift work: outcome miscarriage (adjusted)

3C Comparison of night work with non-shift work: outcome miscarriage (unadjusted)

3D Comparison of night work with non-shift work: outcome miscarriage (adjusted)

Supplementary files:

1: Standard data extraction form

Standard set of information extracted from papers

2: Example search string

(Database: Ovid MEDLINE)

3: Electronic sources

4: Shift definitions

5: Excluded studies

6: Newcastle-Ottawa assessment

Newcastle-Ottawa assessment of studies: allocation of points (‘stars’)

References

1. Women's Business Council. Maximising women’s contribution to future economic growth. London; 2013.

2. The Office of National Statistics. Changes in shift work patterns over the last ten years (1999 to 2009). London: Health and Safety Executive; 2011.

3. Puttonen S, Harma M, Hublin C. Shift work and cardiovascular disease - pathways from circadian stress to morbidity. Scandinavian journal of work, environment & health 2010 Mar;36(2):96-108.

4. Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. Night work and breast cancer: a population-based case-control study in France (the CECILE study). Int J Cancer 2013 Feb 15;132(4):924-31.

5. Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003 Mar;53(2):103-8.

6. NHS Plus. Physical and shift work in pregnancy: Occupational aspects of management : a national guideline. London: Royal College of Physicians of London; 2009.

7. Palmer KT, Bonzini M, Bonde JP. Pregnancy: occupational aspects of management: concise guidance. Clin Med 2013 Feb;13(1):75-9.

8. Bonde JP, Jorgensen KT, Bonzini M, Palmer KT. Miscarriage and occupational activity: a systematic review and meta-analysis regarding shift work, working hours, lifting, standing, and physical workload. Scandinavian journal of work, environment & health 2013 Jul;39(4):325-34.

9. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000 Apr 19;283(15):2008-12.

10. Belsey EM, Pinol AP. Menstrual bleeding patterns in untreated women. Task Force on Long-Acting Systemic Agents for Fertility Regulation. Contraception 1997 Feb;55(2):57-65.

11. National Institute for Health and Clinical Excellence. Fertility: Assessment and treatment for people with fertility problems (update). Clinical guideline 156. guidance.nice.org.uk/cg156; 2013.

12. Farquharson RG, Jauniaux E, Exalto N. Updated and revised nomenclature for description of early pregnancy events. Hum Reprod 2005 Nov;20(11):3008-11.

13. Collaboration TC. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 ed. <http://handbook.cochrane.org;> 2011.

14. Wells G, Shea,B O'Connell, D Peterson, J Welch,V Losos, M Tugwell, P The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp>.

15. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 1959 Apr;22(4):719-48.

16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986 Sep;7(3):177-88.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj 2003 Sep 6;327(7414):557-60.

18. The Royal College of Nursing. A shift in the right direction: RCN guidance on the occupational health and safety of shift work in the nursing workforce. London, UK: The Royal College of Nursing; 2012.

19. Chung FF, Yao CC, Wan GH. The associations between menstrual function and life style/working conditions among nurses in Taiwan. J Occup Health 2005 Mar;47(2):149-56.

20. Lawson CC, Whelan EA, Lividoti Hibert EN, Spiegelman D, Schernhammer ES, Rich-Edwards JW. Rotating shift work and menstrual cycle characteristics. Epidemiology 2011 May;22(3):305-12.

21. Su SB, Lu CW, Kao YY, Guo HR. Effects of 12-hour rotating shifts on menstrual cycles of photoelectronic workers in Taiwan. Chronobiology international 2008 Apr;25(2):237-48.

22. Bisanti L, Olsen J, Basso O, Thonneau P, Karmaus W. Shift work and subfecundity: a European multicenter study. European Study Group on Infertility and Subfecundity. J Occup Environ Med 1996 Apr;38(4):352-8.

23. Spinelli A, Figa-Talamanca I, Osborn J. Time to pregnancy and occupation in a group of Italian women. Int J Epidemiol 1997 Jun;26(3):601-9.

24. Tuntiseranee P, Olsen J, Geater A, Kor-anantakul O. Are long working hours and shiftwork risk factors for subfecundity? A study among couples from southern Thailand. Occup Environ Med 1998 Feb;55(2):99-105.

25. Axelsson G, Ahlborg G, Jr., Bodin L. Shift work, nitrous oxide exposure, and spontaneous abortion among Swedish midwives. Occup Environ Med 1996 Jun;53(6):374-8.

26. Axelsson G, Lutz C, Rylander R. Exposure to solvents and outcome of pregnancy in university laboratory employees. Br J Ind Med 1984 Aug;41(3):305-12.

27. Eskenazi B, Fenster L, Wight S, English P, Windham GC, Swan SH. Physical exertion as a risk factor for spontaneous abortion. Epidemiology 1994 Jan;5(1):6-13.

28. Hemminki K, Kyyronen P, Lindbohm ML. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. J Epidemiol Community Health 1985 Jun;39(2):141-7.

29. Hatch MC, Figa-Talamanca I, Salerno S. Work stress and menstrual patterns among American and Italian nurses. Scandinavian journal of work, environment & health 1999 Apr;25(2):144-50.

30. Whelan EA, Lawson CC, Grajewski B, Hibert EN, Spiegelman D, Rich-Edwards JW. Work schedule during pregnancy and spontaneous abortion. Epidemiology 2007 May;18(3):350-5.

31. Fenster L, Hubbard AE, Windham GC, Waller KO, Swan SH. A prospective study of work-related physical exertion and spontaneous abortion. Epidemiology 1997 Jan;8(1):66-74.

32. Lawson CC, Rocheleau CM, Whelan EA, Lividoti Hibert EN, Grajewski B, Spiegelman D, et al. Occupational exposures among nurses and risk of spontaneous abortion. American journal of obstetrics and gynecology 2012 Apr;206(4):327 e1-8.

33. Zhu JL, Hjollund NH, Boggild H, Olsen J. Shift work and subfecundity: a causal link or an artefact? Occup Environ Med 2003 Sep;60(9):E12.

34. Axelsson G, Rylander R, Molin I. Outcome of pregnancy in relation to irregular and inconvenient work schedules. Br J Ind Med 1989 Jun;46(6):393-8.

35. Attarchi MS, Ashouri M, Labbafinejad Y, Mohammadi S. Assessment of time to pregnancy and spontaneous abortion status following occupational exposure to organic solvents mixture. Int Arch Occup Environ Health 2012 Apr;85(3):295-303.

36. Chen PC, Hsieh GY, Wang JD, Cheng TJ. Prolonged time to pregnancy in female workers exposed to ethylene glycol ethers in semiconductor manufacturing. Epidemiology 2002 Mar;13(2):191-6.

37. Grundy A, Richardson H, Burstyn I, Lohrisch C, Sengupta SK, Lai AS, et al. Increased risk of breast cancer associated with long-term shift work in Canada. Occup Environ Med 2013 Jul 1.

38. McMichael AJ. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. Journal of occupational medicine : official publication of the Industrial Medical Association 1976 Mar;18(3):165-8.

39. Flo E, Pallesen S, Mageroy N, Moen BE, Gronli J, Hilde Nordhus I, et al. Shift work disorder in nurses--assessment, prevalence and related health problems. PLoS One 2012;7(4):e33981.

40. Wang JX, Davies MJ, Norman RJ. Obesity increases the risk of spontaneous abortion during infertility treatment. Obes Res 2002 Jun;10(6):551-4.

41. Cnattingius S, Signorello LB, Anneren G, Clausson B, Ekbom A, Ljunger E, et al. Caffeine intake and the risk of first-trimester spontaneous abortion. The New England journal of medicine 2000 Dec 21;343(25):1839-45.

42. Ballantyne JW. The Problem of the Premature Infant. Br Med J 1902 May 17;1(2159):1196-200.

43. Baba S, Noda H, Nakayama M, Waguri M, Mitsuda N, Iso H. Risk factors of early spontaneous abortions among Japanese: a matched case-control study. Hum Reprod 2011 Feb;26(2):466-72.

44. Ness RB, Grisso JA, Hirschinger N, Markovic N, Shaw LM, Day NL, et al. Cocaine and tobacco use and the risk of spontaneous abortion. The New England journal of medicine 1999 Feb 4;340(5):333-9.

45. Madsen M, Jorgensen T, Jensen ML, Juhl M, Olsen J, Andersen PK, et al. Leisure time physical exercise during pregnancy and the risk of miscarriage: a study within the Danish National Birth Cohort. BJOG 2007 Nov;114(11):1419-26.

46. Revonta M, Raitanen J, Sihvo S, Koponen P, Klemetti R, Mannisto S, et al. Health and life style among infertile men and women. Sex Reprod Healthc 2010 Aug;1(3):91-8.

47. Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. Proc Natl Acad Sci U S A 1972 Jun;69(6):1583-6.

48. Richards J, Gumz ML. Advances in understanding the peripheral circadian clocks. FASEB J 2012 Sep;26(9):3602-13.

49. Sellix MT, Menaker M. Circadian clocks in mammalian reproductive physiology: effects of the "other" biological clock on fertility. Discov Med 2011 Apr;11(59):273-81.

50. Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C. Circadian typology: a comprehensive review. Chronobiology international 2012 Nov;29(9):1153-75.

51. Cooper GS, Ephross SA, Weinberg CR, Baird DD, Whelan EA, Sandler DP. Menstrual and reproductive risk factors for ischemic heart disease. Epidemiology 1999 May;10(3):255-9.

52. Shapley M, Jordan K, Croft PR. An epidemiological survey of symptoms of menstrual loss in the community. The British journal of general practice : the journal of the Royal College of General Practitioners 2004 May;54(502):359-63.

53. National Institute for Health and Clinical Excellence. Ectopic pregnancy and miscarriage: Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. [http://www.nice.org.uk/nicemedia/live/14000/61854/61854.pdf;](http://www.nice.org.uk/nicemedia/live/14000/61854/61854.pdf) 2012.

54. The Secretary of State. The Working Time Regulations 1998. [http://www.legislation.gov.uk/uksi/1998/1833/contents/made;](http://www.legislation.gov.uk/uksi/1998/1833/contents/made) 1998.

55. Equal Opportunities Comission. Greater expectations: summary final report: EOC's investigation into pregnancy discrimination. Manchester; 2005.